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(54) Phenoxyacetic acid derivatives and pharmaceutical compositions containing them

Phenoxyessigsäurederivate und diese enthaltende pharmazeutische Zusammenstellungen

Dérivés d'acide phénoxyacétique et compositions pharmaceutiques les contenant

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(73) Proprietor: **ONO PHARMACEUTICAL CO., LTD.**
Osaka-shi Osaka (JP)

(72) Inventors:
- **Hamanaka, Nobuyuki,**
  c/o Ono Pharmacuetical Co. Ltd
  Mishima-gun, Osaka (JP)
- **Takahashi, Kanji,**
  c/o Ono Pharmacuetical Co., Ltd.
  Mishima-gun, Osaka (JP)
- **Tokumoto, Hidekado,**
  c/o Ono Pharmacuetical Co. Ltd
  Mishima-gun, Osaka (JP)

(74) Representative: **Henkel, Feiler, Hänzel & Partner**
Möhlstrasse 37
81675 München (DE)

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FR-A- 2 434 155
US-A- 5 021 415

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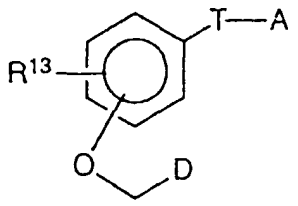
Description

Summary

This invention is related to phenoxyacetic acid derivatives.
More particularly, this invention is related to:

1) phenoxyacetic acid derivatives of the formula (I):

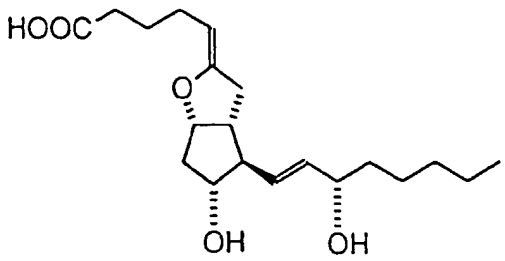


(I)

wherein all the symbols are the same meaning as hereafter defined, and non-toxic salts thereof and non-toxic acid addition salts thereof,
2) processes for the preparation thereof, and
3) pharmaceutical agents containing them as active ingredient.

Background of the Invention

Prostaglandin I_2 (PGI_2) is a physiologically active natural substance having the following structural formula, which is biosynthesized from Prostaglandin H_2 (PGH_2) in the metabolic process in vivo called arachidonate cascade.



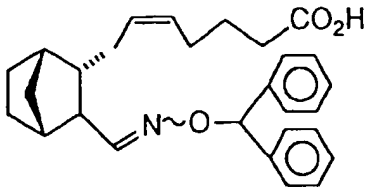
(see Nature, 263, 663(1976), Prostaglandins, 12, 685(1976), *ibid*, 12, 915(1976), *ibid*, 13, 375(1977) and Chemical and Engineering News, Dec. 20, 17(1976)).

PGI_2 has been confirmed to possess not only a very strong inhibitory activity on blood platelet aggregation but a dissociative activity on blood platelet aggregation, an inhibitory activity on blood platelet adhesion, a vasodilating activity, an inhibitory activity on gastric acid secretion etc. Therefore, it has been considered that PGI_2 is useful for the prevention and/or the treatment for thrombosis, arteriosclerosis, ischemic heart diseases, gastric ulcer, hypertension etc. But its application for pharmaceuticals is limited because of its chemical instability and difficulty of separation of the actions according to purpose. Accordingly, various PGI_2 derivatives have been synthesized and many researches have been carried out for the maintenance and the separation of the actions. However, we have not necessarily satisfactory results yet.

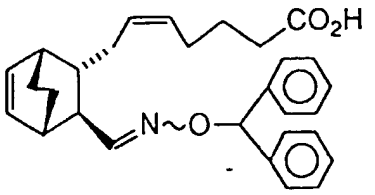
Recently, in order to solve two problems above described, the research for PGI_2 receptor agonists which have a new-typed skeleton and may be useful for the treatment of or for the prevention of the above diseases, in view of PGI_2 receptor level, has been carried out.

Related Arts

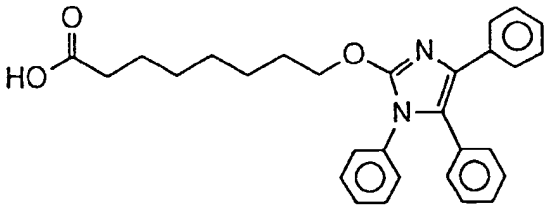
It has been reported in the literatures, that the following compounds not having the PGI_2 skeleton are PGI_2 receptor agonists which bind to a PGI_2 receptor and inhibit blood platelet aggregation:



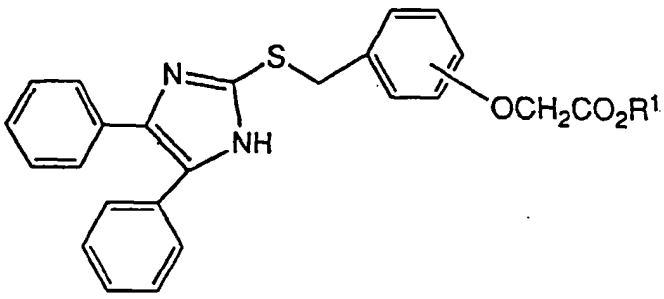
(see Brit. J. Pharmacol., 76, 423(1982), *ibid*, 84, 595(1985), and the Japanese Patent Kohyo No. 55-501098),



(see Brit. J. Pharmacol., 76, 423(1982), *ibid*, 84, 595(1985), and the Japanese Patent Kohyo No. 57-501127),



(see Brit. J. Pharmacol., 102, 251-266(1991) and the West German Patent Publication No. 3,504,677), and



(see United States Patent No. 5,011,851).

EP-A-0,442,448 and one of the priority documents thereto (viz. US-A-5,021,415) disclose heterocyclic carboxylic acids of the phenoxyacetic acid type which are said to possess inhibitory activity on blood platelet aggregation. Said heterocyclic carboxylic acids differ from the claimed phenoxyacetic acid derivatives of formula (I) in the type and/or substitution of the heterocycle.

Purpose of the Invention

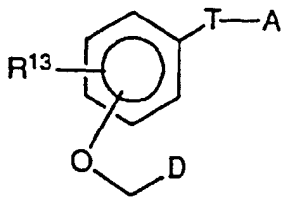
Energetic investigations have been carried out in order to discover new PGI_2 receptor agonists having a skeleton in chemical structure different from the compounds mentioned above, the present inventors have found that a kind of phenoxyacetic acid derivatives has an activity on binding to PGI_2 receptor and an inhibitory activity on blood platelet aggregation, and have accomplished the present invention.

The phenoxyacetic acid derivatives of the formula (I), of the present invention are quite novel, and it is not easy to predict from the above compounds already known as PGI_2 receptor agonist, that the compounds of the present invention have an activity of PGI_2 receptor agonist.

Detailed disclosure of the Invention

The present invention is related to :

1) Phenoxyacetic acid derivatives of the formula (I):



(I)

wherein

A is
i) $-CR^1=N\sim OR^2$,
ii) $-CHR^1-NH-OR^2$,
iii) -COE,
iv) $-SO_2E$,
v) $-CH_2-NR^3-Y$,
vi) $-Z-NR^3-CONR^4R^5$,
vii) $-CH_2-OR^6$,
viii) $-CO_2R^6$,
ix) $-CH_2-O\sim N=CR^7R^8$ or
x) $-CH_2-O-NHCHR^7R^8$,

T is
i) single bond,
ii) C1-6 alkylene,
iii) C2-6 alkenylene or
iv) $-O(CH_2)_s-$;

D is
i) $-CO_2R^{10}$ or
ii)$-CONR^{11}R^{12}$;

E is
i) $-NR^4R^5$,
ii) $-NR^3OR^6$,
iii) $-NR^3-NR^4R^5$ or
iv) $-NR^3-N=CR^4R^5$;

Y is
i) $-COR^6$,
ii) -CO-L-NR^4R^5,
iii) -CS-NHR^4 or
iv) $-SO_2R^6$;

Z is
i) -CH=N- or
ii) $-CH_2-NR^3-$;

L is single bond or C1-4 alkylene;

R^1 is hydrogen, C1-6 alkyl or phenyl;

R^2 is
i) C1-8 alkyl substituted by one or two of phenyl, 4-7 membered monocyclic hetero ring containing one nitrogen or C4-7 cycloalkyl,
ii) C10-15 hydrocarbon condensed tricyclic ring or

iii) C1-15 alkyl;

R^3	is hydrogen, C1-6 alkyl or phenyl;
R^4 and R^5 each, independently, is	i) hydrogen, ii) phenyl, iii) 4-7 membered monocyclic hetero ring containing one nitrogen or iv) C1-4 alkyl substituted by one or two of phenyl or 4-7 membered monocyclic hetero ring containing one nitrogen;
R^6 is	i) phenyl, ii) 4-7 membered monocyclic hetero ring containing one nitrogen or iii) C1-4 alkyl substituted by one to three of phenyl or 4-7 membered monocyclic hetero ring containing one nitrogen;
R^7 is	i) hydrogen, ii) C1-8 alkyl, iii) phenyl or C4-7 cycloalkyl, iv) 4-7 membered monocyclic hetero ring containing one nitrogen or v) C1-4 alkyl substituted by one or two of phenyl, C4-7 cycloalkyl or 4-7 membered monocyclic hetero ring containing one nitrogen;
R^8 is	i) C1-8 alkyl, ii) phenyl or C4-7 cycloalkyl iii) 4-7 membered monocyclic hetero ring containing one nitrogen or iv) C1-4 alkyl substituted by one or two of phenyl, C4-7 cycloalkyl or 4-7 membered monocyclic hetero ring containing one nitrogen;
R^{10} is	hydrogen or C1-12 alkyl;
R^{11} and R^{12}	each, independently, is hydrogen or C1-4 alkyl or
R^{11} and R^{12},	taken together with nitrogen bond to R^{11} and R^{12} is the residue of an amino acid;
R^{13} is	hydrogen, C1-4 alkyl, C1-4 alkoxy or nitro;
s is	2-4;

and the rings of R^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^8 may be also substituted by one to three of C1-C4 alkyl, C1-C4 alkoxy, halogen, nitro or trihalomethyl;

with the proviso that,

(1) when A is $-SO_2E$ wherein E is the same meaning hereinbefore defined, T is not single bond and C1 alkylene (methylene),
(2) the compounds wherein A is -CONH-phenyl (phenyl may be substituted by 1-3 of C1-4 alkyl, C1-4 alkoxy, halogen or NO_2) are excluded,

and non-toxic salts thereof and non-toxic acid addition salts thereof.

2) Process for the preparation of them and

3) Pharmaceutical agent containing them as active ingredient.

Unless otherwise, specified all isomers are included in the invention. For example, alkyl, alkoxy, alkylene and alkenylene includes straight and branched ones. Double bond in alkenylene and oxime include E, Z and EZ mixture. Isomers generated by asymmetric carbon(s) e.g. branched alkyl are included in the present invention.

The compounds of the formula (I) of the present invention, wherein R^{10} is hydrogen may be converted into the

corresponding salts by methods known per se. Non-toxic and water-soluble salts are preferable. Suitable salts, for example, are salts of alkaline metal (potassium, sodium, etc.), salts of alkaline earth metal (calcium, magnesium, etc.), ammonium salts, salts of pharmaceutically-acceptable organic amine (tetramethylammonium, triethylamine, methylamine, dimethylamine, cyclopentylamine, benzylamine, phenethylamine, piperidine, monoethanolamine, diethanolamine, tris(hydroxymethyl)amine, lysine, arginine, N-methyl-D-glucamine, etc.).

The compounds of the formula (I) may be converted into the corresponding acid additional salts by methods known per se. Non-toxic and water-soluble salts are preferable. Suitable acid addition salts, for example, are salts of inorganic acids, e.g., hydrochloride, hydrobromide, sulphate, phosphate, nitrate etc., or salts of organic acids, e.g., acetate, lactate, tartarate, oxalate, fumarate, maleate, citrate, benzoate, methanesulphonate, ethanesulphonate, benzenesulphonate, toluenesulphonate, isethioate, glucuronate, gluconate etc.

The compounds of the formula (I), salts thereof or acid additional salts thereof may be converted into hydrate thereof by methods known per se.

In the formula (I), C1-4 alkylene represented by L means methylene, ethylene, trimethylene, tetramethylene and isomeric groups thereof. C1-6 alkylene represented by T means methylene, ethylene, trimethylene, tetrametylene, pentamethylene, hexamethylene and isomeric groups thereof. C2-6 alkenylene represented by T means ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene and isomeric groups thereof having one or two double bond.

In the formula (I), C1-4 alkyl represented by R^4, R^5, R^6, R^7, R^8, R^{11}, R^{12} and R^{13} mean methyl, ethyl, propyl, butyl and isomeric groups thereof. C1-6 alkyl represented by R^1 and R^3 mean methyl, ethyl, propyl, butyl, pentyl, hexyl and isomeric groups thereof. C1-8 alkyl represented by R^2, R^7 and R^8 mean methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl and isomeric groups thereof. C1-15 alkyl represented by R^2 means methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl and isomeric groups thereof. C1-12 alkyl represented by R^{10} means methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl and isomeric groups thereof.

In the formula (I), C1-4 alkoxy represented by R^{13} means methoxy, ethoxy, propoxy, butoxy and isomeric groups thereof.

In the formula (I), C4-7 cycloalkyl represented by R^2, R^7 and R^8 mean, for example, cyclopentyl, cyclohexyl and cycloheptyl.

In the formula (I), 4-7 membered monocyclic hetero ring represented by R^2, R^4, R^5, R^6, R^7 and R^8 mean, for example, pyrrole, pyridine, azepine ring and partially or fully saturated ring thereof (e.g., pyrrolidine, piperidine ring, etc.).

In the formula (I), C10-15 hydrocarbon condensed tricyclic ring means, for example, indacene, fluorene, anthracene, dibenzocycloheptene rings and partially or fully saturated ring thereof.

In the formula (I), C1-C4 alkyl as substituents of the rings in R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 mean methyl, ethyl, propyl, butyl and isomers thereof. C1-C4 alkoxy mean methoxy, ethoxy, propoxy, butoxy and isomers thereof. Halogen and halogen in trihalomethyl mean fluorine, chlorine, bromine and iodine atoms.

Example of representative compounds of the formula (I), of the present invention are listed as follows:

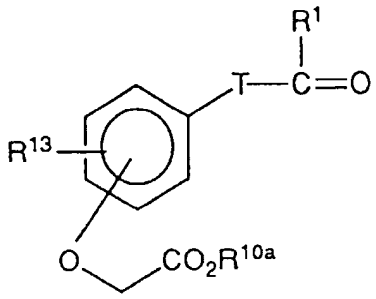
(1) 3-[2-[2-Phenyl-2-(3-pyridyl)ethyl]oxyiminoethyl]phenoxyacetic acid,
(2) 3-[2-(2-Cyclohexyl-2-phenylethyl)oxyiminoethyl]phenoxyacetic acid,
(3) 3-[2-[2-(Fluorene-9-yl)ethyl]oxyiminoethyl]phenoxyacetic acid,
(4) 3-[2-(2-Phenyldecyl)oxyiminoethyl]phenoxyacetic acid,
(5) 4-(2-Benzoylaminoethyl)phenoxyacetic acid,
(6) 4-[2-(N,N-Diphenylaminocarbonylamino)ethyl]phenoxyacetic acid,
(7) 4-[2-(N,N 4-[2-(N,N-Diphenylaminomethylcarbonylamino)ethyl]phenoxyacetic acid,
(8) 4-(2-Phenylaminothiocarbonylaminoethyl)phenoxyacetic acid,
(9) 4-(2-Phenylsulfonylaminoethyl)phenoxyacetic acid,
(10) 4-[2-(N,N-Diphenylaminocarbonylaminoimino)ethyl]phenoxyacetic acid,
(22) 3-[3-Di(3-pyridyl)methyloxyiminopropyl]phenoxyacetic acid,
(23) 3-[3-[Di(3-pyridyl)methylideneaminooxy]propyl]phenoxyacetic acid,
(24) 3-[3-[1-Cyclohexyl-1-phenylmethylideneaminooxy]propyl]phenoxyacetic acid,
(25) 2-Methyl-3-[3-[1-phenyl-1-(3-pyridyl)methylideneaminooxy]propyl]-phenoxyacetic acid,
(26) 3-(3-Diphenylmethyloxyaminosulfonylpropyl)phenoxyacetic acid,
(27) 3-[3-[(N,N-Diphenylamino)aminosulfonyl]propyl]phenoxyacetic acid,
(28) 3-[3-[(1,1-Diphenylmethylideneamino)aminosulfonyl)propyl]phenoxy acetic acid,
(29) 4-[2-[(N,N-Diphenylaminocarbonylamino)amino]ethyl]phenoxyacetic acid,
(31) 3-[4-Methyl-4-(1-phenyl-1-(3-pyridyl)methyloxyimino)butyl]phenoxyacetic acid,
(33) 3-[3-[1-Phenyl-1-(3-pyridyl)methylaminooxy]propyl]phenoxyacetic acid, non-toxic salts thereof and non-toxic

acid addition salts thereof and those description in examples below.

Process for the preparation

The compounds of the present invention of the formula (I), may be prepared:

(i) by reacting a compound of the formula (III):

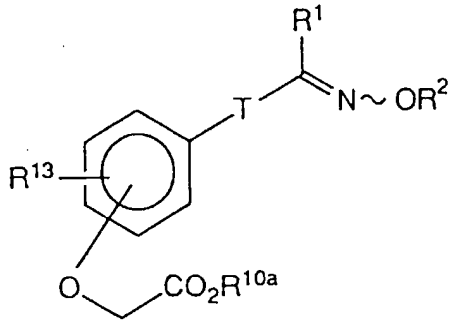


(III)

wherein R^{10a} menas methyl or ethyl and the other symbols are the same meaning as hereinbefore defined, with a compound of the formula (a):

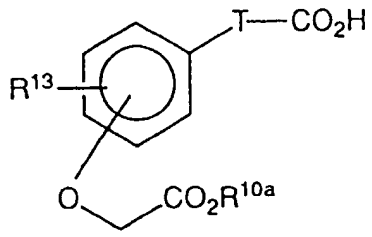
$$R^2ONH_2 \qquad (a)$$

wherein R^2 is the same meaning as hereinbefore defined,
(ii) by subjecting a compound obtained by reaction (i) of the formula (Ia-1):



(Ia-1)

wherein all the symbols are the same meaning as hereinbefore defined, to reduction,
(iii) by amidation of a compound of the formula (IV):

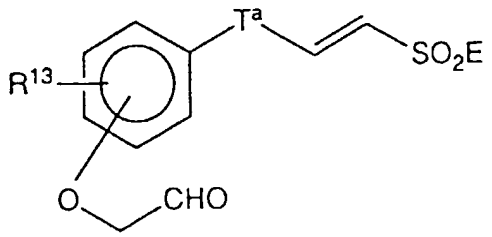


(IV)

wherein all the symbols are the same meaning as hereinbefore defined, with a compound of the formula (b):

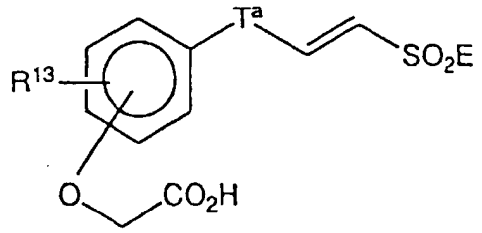
H E (b)

wherein E is the same meaning as hereinbefore defined,
(iv) by subjecting a compound of the formula (VI):



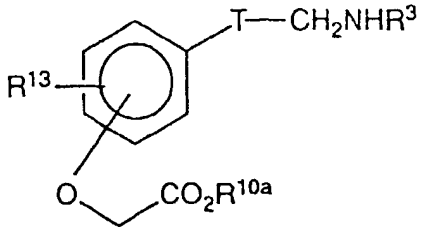
(VI)

wherein T^a is single bond, C1-4 alkylene, C2-4 alkenylene, or -O-$(CH_2)_t$-wherein t is 0-2, and the other symbols are the same meaning as hereinbefore defined, to Jone's oxidation,
(v) by subjecting a compound obtained by reaction (iv) of the formula (Ib-1):



(Ib-1)

wherein all the symbols are the same meaning as hereinbefore defined, to hydrogenation (including a series of reactions subjecting a compound of the formula (Ib-1) to methylesterification, and to hydrogenation, followed by hydrolysis of the ester bond, for the convenience of purification),
(vi) by amidation or thioamidation of a compound of the formula (VIII):



(VIII)

wherein all the symbols are the same meaning as hereinbefore defined, with a compound of the formula (c):

$$R^6CO_2H \quad (c)$$

wherein R^6 is the same meaning as hereinbefore defined, or with a compound of the formula (d):

$$R^4R^5N\text{-}L\text{-}CO_2H \quad (d)$$

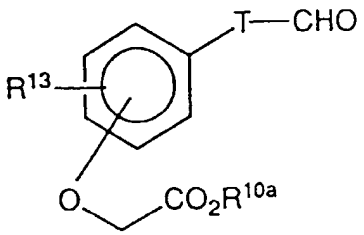
wherein all the symbols are the same meaning as herein before defined, or with a compound of the formula (e):

$$R^4\text{-}N{=}C{=}S \qquad (e)$$

wherein R^4 is the same meaning as hereinbefore defined, or with a compound of the formula (f):

$$R^6SO_2Cl \qquad (f)$$

wherein R^6 is the same meaning as hereinbefore defined,
(vii) by reacting a compound of the formula (VII):

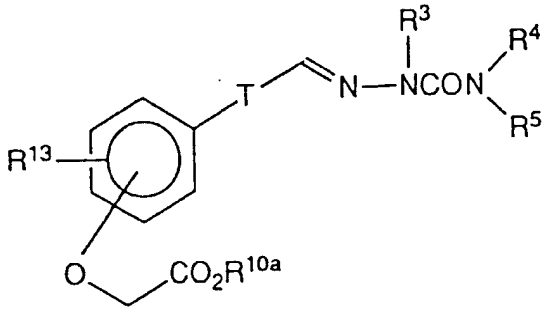


(VII)

wherein all the symbols are the same meaning as hereinbefore defined, with a compound of the formula (g):

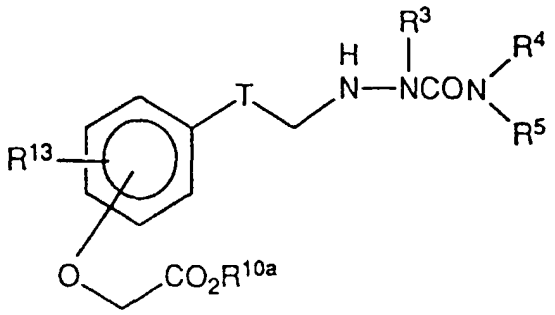
$$H_2N\text{-}NR^3\text{-}CONR^4R^5 \qquad (g)$$

wherein all the symbols are the same meaning as hereinbefore defined,
(viii) by subjecting a compound obtained by reaction (vii) of the formula (Ia-5):



(Ia-5)

wherein all the symbols are the same meaning as hereinbefore defined, to reduction,
(ix) by reacting of the compound obtained by reaction (viii) of the formula (Ia-6):

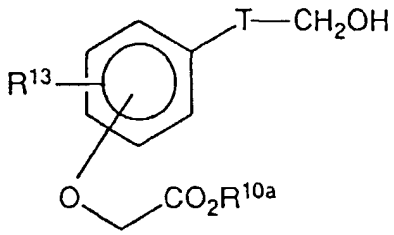


(Ia-6)

wherein all the symbols are the same meaning as hereinbefore defined, with a compound of the formula (h):

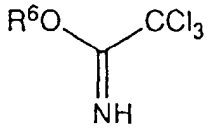
$$R^{3a}\text{-}I \qquad \text{(h)}$$

wherein R^{3a} is C1-6 alkyl or phenyl,
(x) by reacting of the compound of the formula (II):



(II)

wherein all the symbols are the same meaning as hereinbefore defined, with a compound of the formula (i):

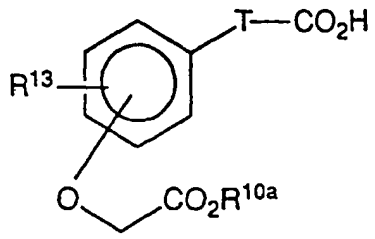


(i)

wherein R^6 is the same meaning as hereinbefore defined, or with a compound of the formula (s):

$$R^6\text{-}X \qquad \text{(s)}$$

wherein X is halogen and R^6 is the same meaning as hereinbefore defined,
(xi) by esterification of a compound of the formula (IV):

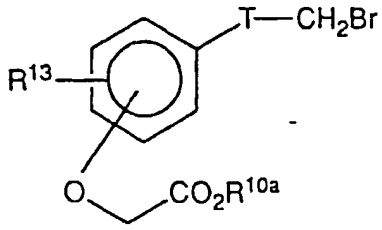


(IV)

wherein all the symbols are the same meaning as hereinbefore defined, with a compound of the formula (j):

$$R^6OH \qquad (j)$$

wherein R^6 is the same meaning as hereinbefore defined,
(xii) by reacting of a compound of the formula (IX):



(IX)

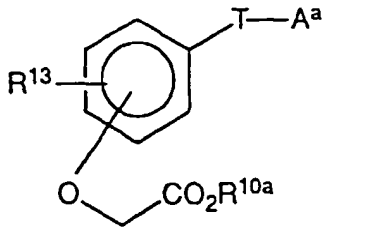
wherein all the symbols are the same meaning as hereinbefore defined, with a compound of the formula (q):

$$HO{\sim}N{=}CR^7R^8 \qquad (q)$$

wherein all the symbols are the same meaning a hereinbefore defined, or with a compound of the formula (r):

$$HO\text{-}NH\text{-}CHR^7R^8 \qquad (r)$$

wherein all the symbols are the same meaning as hereinbefore defined,
(xiii) by hydrolysis of the compound obtained by hereinbefore reaction (i), (ii), (iii), (vi), (vii), (viii), (ix), (x), (xi) or (xii) of the formula (Ia):

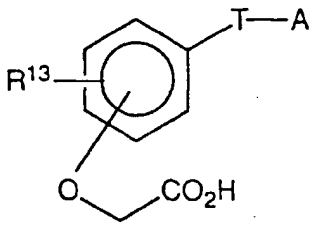


(Ia)

wherein

A^a is
i) $-CR^1=N\sim OR^2$,
ii) $-CHR^1-NH-OR^2$,
iii) -COE,
iv) $-CH_2NR^3-Y$,
v) $-CH=N-NR^3-CONR^4R^5$,
vi) $-CH_2-NH-NR^3-CONR^4R^5$,
vii) $-CH_2-NR^{3a}-NR^3-CONR^4R^5$,
viii) $-CH_2OR^6$,
ix) $-CO_2R^6$,
x) $-CH_2-O\sim N=CR^7R^8$ or
xi) $-CH_2-O-NHCHR^7R^8$,

and the other symbols are the same meaning as hereinbefore defined,
(xiv) by esterification of the compound obtained by hereinbefore reaction (iv) or (v) of the formula (Ib):

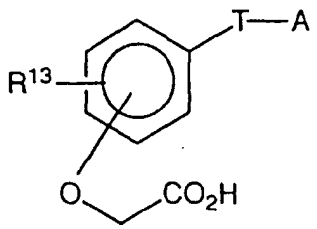


(Ib)

wherein all the symbols are the same meaning as hereinbefore defined, with a compound formula (o):

$$R^{10b}OH \qquad (o)$$

wherein R^{10b} is C1-12 alkyl, or
(xv) by amidation of the compound obtained hereinbefore reaction (iv) or (v) of the formula (Ib):



(Ib)

wherein all the symbols are the same meaning as hereinbefore defined, with a compound formula (p):

$$R^{11}R^{12}NH \qquad (p)$$

wherein all the symbols are the same meaning as hereinbefore defined.

The reaction (i) is known, for example, it may be carried out in an inert organic solvent (tetrahydrofuran (THF), methanol, ethanol, dimethoxyethane, dioxane or two or more of the mixture, etc.) at 0-70°C.

The reaction (ii) and (viii) are known, for example, they may be carried out in a water miscible organic solvent (THF, dioxane, methanol, ethanol, dimethoxyethane or two or more of the mixture, etc.), in the presence of an acid (hydrochloric acid, acetic acid, trifluoroacetic acid, etc.), using a reducing agent (sodium cyanoborohydride, etc.) at 0-70°C.

The reaction (iii) and (vi) are known, for example, they may be carried out in an inert organic solvent (methylene chloride, etc.), in the presence of an appropriate condensing agent (2-chloro-N-methylpyridinum iodide, etc.) and a proper base (triethylamine, N,N-dimethylaminopyridine or two or more of the mixture, etc.) at 0-40°C.

The reaction (iv) is known, for example, it may be carried out in acetone using a Jone's agent at -10-40°C.

The reaction (v) is known, for example, it may be carried out in an inert organic solvent (THF, diethylether, dioxane, ethyl acetate, methanol, ethanol, methylene chloride, etc.) using a catalyst (palladium on carbon, palladium, hydoxy palladium, palladium acetic acid, palladium black, platinum black, etc.) at normal or elevated pressure of hydrogen gas, at 0-80°C.

The reaction may be carried out, for the convenience of purification, the compound of the formula (Ib-1) reacted to methylestification, and to hydrogenation, following hydrolysis of ester bond. The methylestification is known, for example, it may be carried out in an inert organic solvent (diethylether, ethyl acetate, etc.) using diazomethane at 0-10°C. And the hydolysis of ester bond may be carried out by the same procedure as hereafter defined for the reaction (xiii).

The reaction (vii) is known, for example, it may be carried out in an inert organic solvent (methanol, ethanol, etc.) under an atmosphere of inert gas at 0-40°C.

The reaction (ix) is known, for example, it may be carried out in an inert organic solvent (N,N-dimethylformamide (DMF), etc.), in the presence or absence of an appropriate base (sodium hydride, etc.).

The reaction (x) is known, for example, it may be carried out in an inert organic solvent (chloroform, cyclohexane or two or more of the mixture, etc.), in the presence of the Lewis acid (trifluoroborane etherate, etc.), or in an inert organic solvent (DMF, etc.), in the presence of an amine (N,N-dimethylaminopyridine, triethylamine, pyridine, etc.) at 0°C - a reflux temperature.

The reaction (xi) is known, for example, it may be carried out in an inert organic solvent (methylene chloride, etc.), in the presence of an appropriate condensing agent (2-chloro-N-methylpyridinum iodide, etc.) and a proper base (triethylamine, N,N-dimethylaminopyridine or two or more of the mixture etc.) at 0-40°C.

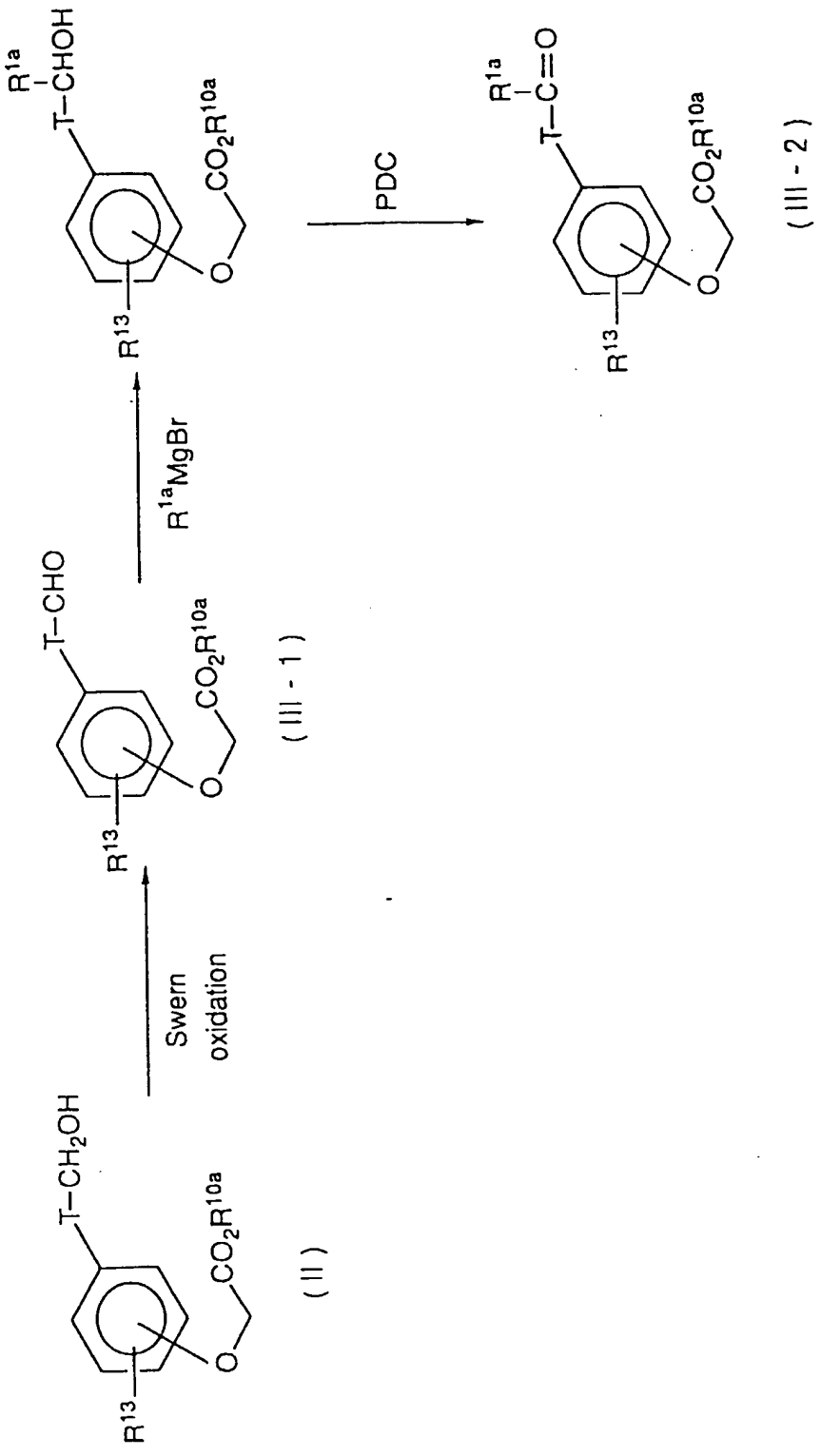
The reaction (xii) is known, for example, it may be carried out in inert organic solvent (DMF, THF, etc.), in present of an appropriate base (sodium hydride, potassium t-butoxide, n- butyllithium, etc.).

The reaction (xiii) is known, for example, it may be carried out in an inert organic solvent (methanol, ethanol, dioxane, THF, dimethoxyethane or two or more of the mixture, etc.) using an aqueous solution of an alkaline (potassium hydroxide, sodium hydroxide, potassium carbonate, sodium carbonate, etc.) at 0- 50°C.

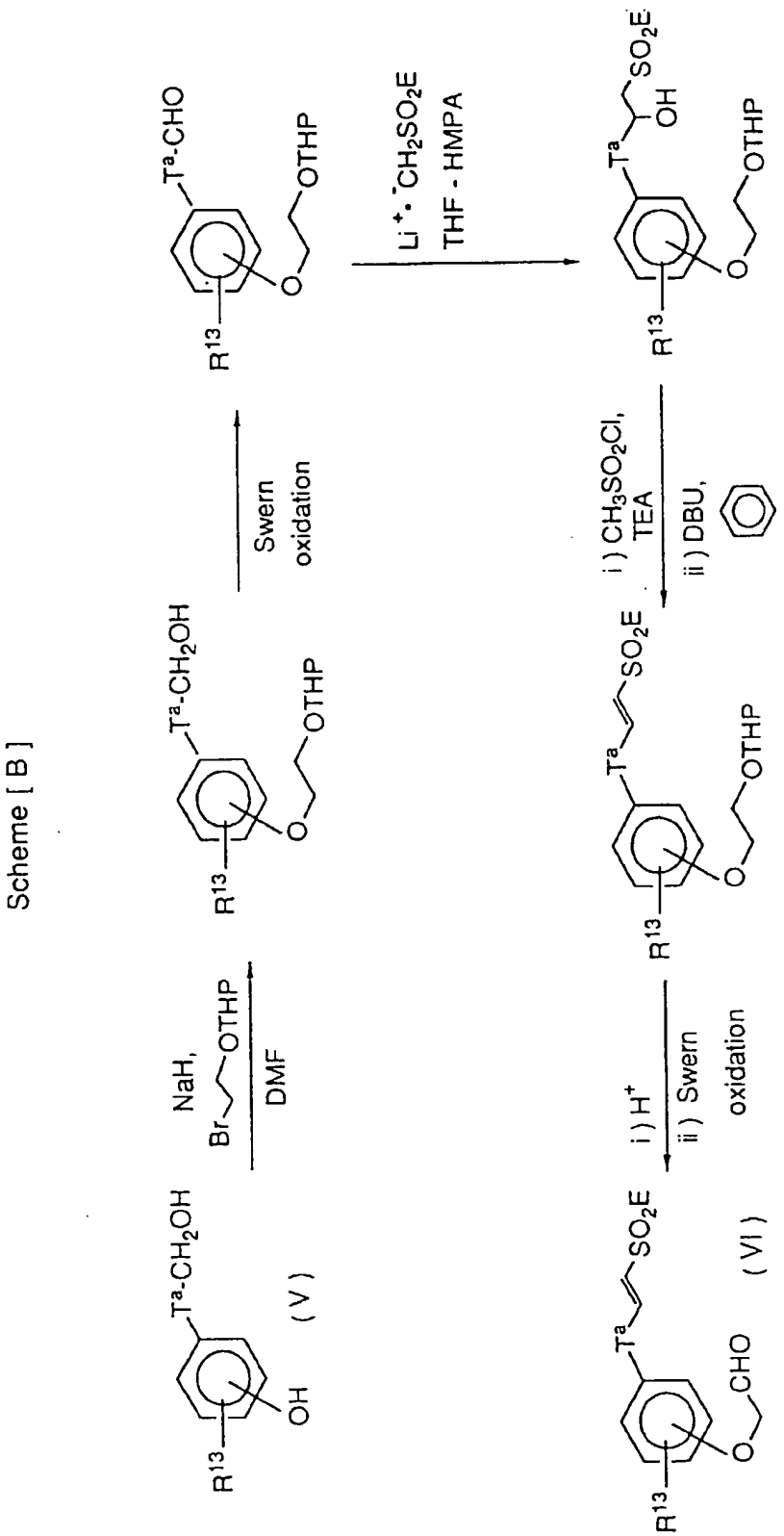
The reaction (xiv) and (xv) are known, for example, they may be carried out by reacting a compound of the formula (Ib) in an inert organic solvent (methylene chloride, etc.) with an acyl halide such as oxalyl chloride, thionyl chloride, and then by reacting a compound thus obtained with an alcohol of the formula (o) or an amine of the formula (p), respecitvely, in an inert organic solvent (methylene chloride, etc.), in the presence of an appropriate base (triethylamine, etc.) at 0-40°C.

Compounds of the formula (III), (VI), (VIII) and (IX) may be prepared by using a series of reactions depicted in the following scheme.

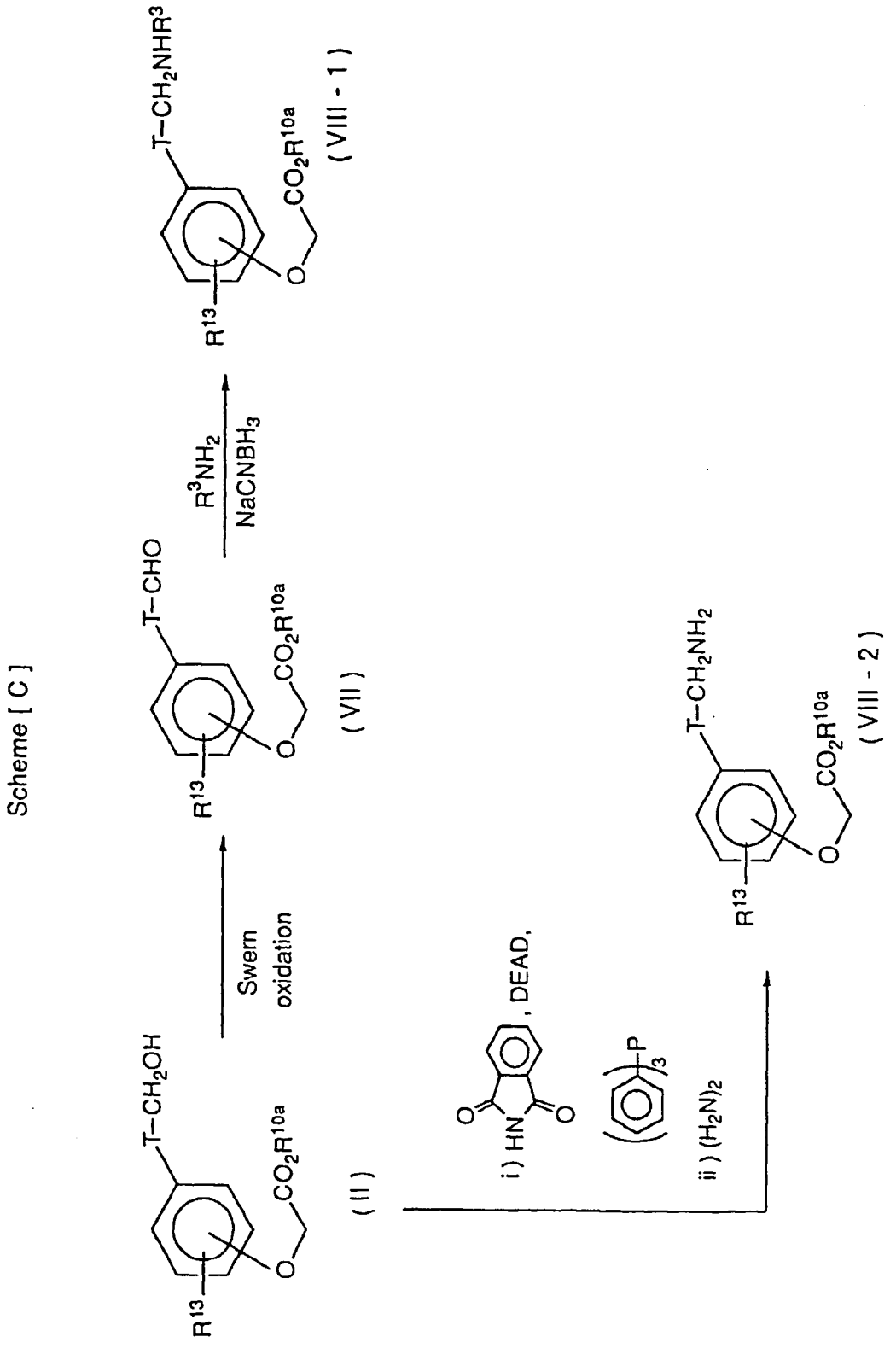
Scheme [A]


T–CH2OH
CO2R10a
R13
Swern oxidation
(II)
T–CHO
CO2R10a
R13
(III - 1)
R1aMgBr
R1a
T–CHOH
CO2R10a
R13
PDC
R1a
T–C=O
CO2R10a
R13
(III - 2)

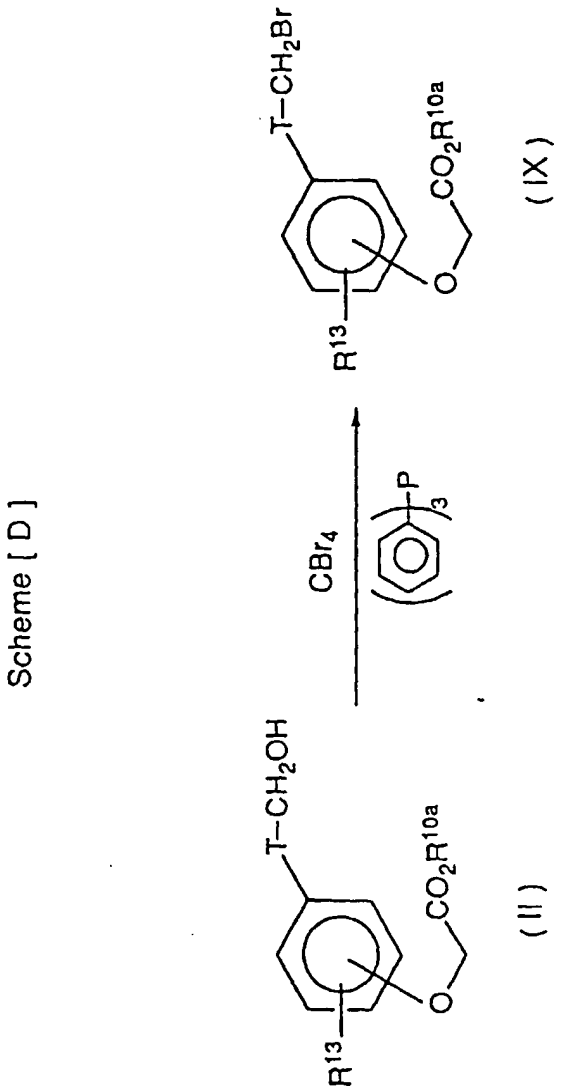
Scheme [B]


Ta-CHO
OTHP
R13
Li+• -CH2SO2E
THF - HMPA
Ta-CH2OH
Swern
oxidation
NaH,
Br
OTHP
DMF
Ta
SO2E
OH
i) CH3SO2Cl,
TEA
ii) DBU,
i) H+
ii) Swern
oxidation
CHO
(V)
(VI)

Scheme [C]


T–CH2OH
CO2R10a
R13
(II)
Swern oxidation
T–CHO
CO2R10a
R13
(VII)
R3NH2
NaCNBH3
T–CH2NHR3
CO2R10a
R13
(VIII - 1)
i) HN
O
O
, DEAD,
P
/3
ii) (H2N)2
T–CH2NH2
CO2R10a
R13
(VIII - 2)

Scheme [D]



In the scheme,

the symbols are the same meaning as hereinbefore defined;
PDC is pyridinium dichromate;
DMF is N,N-dimethylformamide;
THF is tetrahydrofuran;
HMPA is hexamethylphosphoramide;
TEA is triethylamine;
DBU is 1,8-diazabicyclo [5, 4, 0]-7-undecene and
DEAD is diethylazocarboxylate.

In each reaction in the present specification, products may be purified by conventional manner. For example, it may be carried out by distillation at atmospheric or reduced pressure, high performace liquid chromatography, thin layer chromatography or column chromatography using silica gel or magnesium silicate, washing or recrystallization. Purification may be carried out after each reaction, or after a series of reactions.

The starting materials and each reagents in process for the preparation of the present invention are known per se, or may be prepared by methods known per se.

Pharmacological Activities

It has been confirmed that the compounds of the present invention of the formula (I) possess an agonistic activity on PGI_2 receptor by the following experimental results.

i) Inhibitory activity on binding of [^{3}H]-iloprost to PGI_2 receptor on human blood platelet membrane fraction -

Method

50 mM Tris-HCl buffer (pH 7.4) containing 15 mM $MgCl_2$, 5 mM EDTA and 10 nM [^{3}H]-iloprost were used as reaction medium. To 0.2 ml of the reaction medium, human blood platelet membrane fraction (0.3 mg protein) was added with or without a test compound. The mixture was incubated at 24°C for 30 min. After incubation, 4ml of ice-cold 10 mM Tris-HCl buffer (pH 7.4) was added to the reaction mixture, and filtered through Whatman GF/B® glass fiber filter, and washed 4 times with 4 ml of ice-cold 10 mM Tri-HCl buffer (pH 7.4) to separate bound and free [^{3}H]-iloprost. After washing, the filter was dried and radioactivity was counted. Non-specific binding was obtained by performing parallel binding experiments in the presence of 10 μM non-labelled iloprost. Specific binding was calculated by subtracting the non-specific binding from the total binding.

The inhibitory effect of test compound was calculated from the following equation.

$$\text{The percentage of inhibition (\%)} = 100 - (B_1/B_0 \times 100)$$

B_1 : specific [^{3}H]-iloprost binding in presence of test compound
B_0 : specific [^{3}H]-iloprost binding in absence of test compound

The results are shown in the following Table 1.

Table 1

Example No.	IC_{50} (μM)
2	4.8
4	1.6
6	3.0
8(l)	1.5
8(n)	2.0
8(o)	0.46
12	1.3
15	4.0
17(b)	5.0

ii) Inhibitory effect on human blood platelet aggregation

Method

Platelet-rich plasma (PRP) was prepared from human blood (5 X 10^5 platelets / mm^3), and a test compound was added to PRP 1 min prior to the addition of ADP (4 μm). The aggregation was monitored using a platelet aggregometer (NBS HEMA TRACER 601®, Niko Bioscience, Japan).
The results are shown in the following Table 2.

Table 2

Example No.	IC_{50} (μM)
4	3.7
8(n)	3.1
8(o)	0.97
12	5.0

Toxicity

The toxicity of the compounds of the present invention, of the formula (I) is very low and therefore, it may be confirmed that the compounds of the present invention are fully safe for pharmaceutical use.

Application for Pharmaceuticals

The compounds of the present invention, of the formula (I) possess an agonistic activity on PGI2 receptor, and therefore are useful for the prevention and/or the treatment of thrombosis, arteriosclerosis, ischemic heart diseases, gastric ulcer and hypertension, etc.

For the purpose above described, the compounds of the formula (I), of the present invention, non-toxic salts thereof, acid additional salts thereof and hydrates thereof may be normally administered systemically or partially, usually by oral or parenteral administration.

The doses to be administered are determined depending upon age, body weight, symptom, the desired therapeutic effect, the route of administration, and the duration of the treatment etc. In the human adult, the doeses per person per dose are generally between 1 mg and 1000 mg, by oral administration, up to several times per day, and between 100 μg and 100 mg, by parenteral administration up to several times per day, or continuous administration between 1 and 24 hrs. per day from vein.

As mentioned above, the doses to be used depend upon various conditions. Therefore, there are cases in which doses lower than or greater than the ranges specified above may be used.

When administration of the compounds of the present invention, it is used as solid compositions, liquid compositions or other compositions for oral administration, as liniments or suppositories etc. for parenteral administration.

Solid compositions for oral administration include compressed tablets, pills, capsules, dispersible powders, and granules. Capsules include hard capsules and soft capsules.

In such compositions, one or more of the active compound(s) is or are admixed with at least one inert diluent (such as lactose, mannitol, glucose, hydroxypropyl cellulose, microcrystalline cellulose, starch, polyvinylpyrrolidone, magnesium metasilicate aluminate, etc.). The compositions may also comprise, as is normal practice, additional substances other than inert diluents: e.g. lubricating agents (such as magnesium stearate etc.), disintegrating agents (such as cellulose calcium glycolate, etc.), stabilizing agents (such as lactose, etc.), and assisting agents for dissolving such as glutamic acid, etc.).

The tablets or pills may, if desired,-be coated with a film of gastric or enteric material (such as sugar, gelatin, hydroxypropyl cellulose or hydroxypropylmethyl cellulose phtalate, etc.), or be coated with more than two films. And further, coating may include containment within capsules of absorbable materials such as gelatin.

Liquid compositions for oral administration include pharmaceutically-acceptable solutions, emulsions, suspensions, syrups and elixirs. In such compositions, one or more of the acitve compound(s) is or are contained in inert diluent(s) commonly used in the art (Purified water, ethanol etc.). Besides inert diluents, such compositions may also comprise adjuvants (such as wetting agents, suspending agents, etc.), sweetening agents, flavouring agents, perfuming agents, and preserving agents.

Other compositions for oral administration included spray compositions which may be prepared by known methods and which comprise one or more of the active compound(s). Spray compositions may comprise additional substances other than inert diluents: e.g. stabilizing agents (sodium sulfate etc.), isotonic buffer(sodium chloride, sodium citrate, citric acid, etc.). For preparation of such spray compositions, for example, the method described in the United States Patent No. 2,868,691 or 3,095,355 (herein incorporated in their entireties by reference) may be used.

Injections for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions and emulsions. In such compositions, one more of active compounds(s) is or are admixed with at least one of inert aqueous diluent(s) (distilled water for injection, physiological salt solution etc.) or inert non-aqueous diluent(s) (propylene glycol, polyethylene glycol, olive oil, ethanol, POLYSORBATE80 (registered trade mark), etc.).

Injections may comprise additional other than inert diluents: e.g. preserving agents, wetting agents, emulsifying agents, dispersing agents, stabilizing agent (lactose, etc.), assisting agents such as assisting agents for dissolving (glutamic acid, asparaginic acid, etc.).

They may be sterilized for example, by filtration through a bacteria-retaining filter, by incorporation of sterilizing agents in the compositions or by irradiation. They may also be manufactured in the form of sterile solid compositions, for example, by freeze-drying, and which may be dissolved in sterile water or some other sterile diluent(s) for injection immediately before used.

Other compositions for parenteral administration include liquids for external use, and endermic liniments, ointment, suppositories and pessaries which comprise one or more of the active compound(s) and may be prepared by per se known methods.

Reference examples and Examples

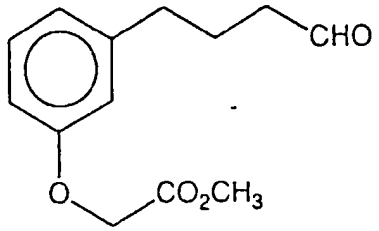
The following reference examples and examples illustrate the present invention, but not limit the present invention.

The solvents in parentheses show the developing or eluting solvents and the ratios of the solvents used are by volume in chromatographic separations.

Unless otherwise specified, "IR" were measured by the liquid film method, and "NMR" were measured in a solution of $CDCl_3$.

Reference example 1

Methyl 3-(3-formylpropyl)phenoxyacetate



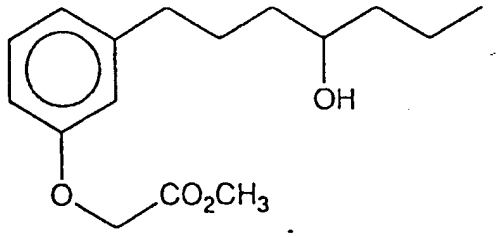
To a solution of oxalyl chloride (1.26 ml) in methylene chloride (30 ml) at -70 °C, a solution of dimethylsulfoxide (2.11 ml) in methylene chloride (3.0 ml) was added dropwise. To the obtained solution, a solution of methyl 3-(4-hydroxybutyl) phenoxyacetate (1.94 g) in methylene chloride (8.0 ml) was added dropwise. Triethylamine (6.9 ml) was added dropwise thereto while the reaction temperature was maintained at -70 °C. The reaction mixture was warmed slowly to -40 °C over a 30 min period and then quenched by addition of a saturated aqueous solution of ammonium chloride. The reaction mixture was extracted with ether. The extract was washed with a saturated aqueous solution of ammonium chloride and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 5 : 2) to give the title compound (1.41 g) having the following physical data.

TLC: Rf 0.26 (n-hexane : ethyl acetate = 2 : 1);

NMR: δ 9.74 (1H, s), 7.35-7.07(1H, m), 6.92-6.60 (3H, m), 4.62 (2H, s), 3.79 (3H, s), 2.63 (2H, t, J=7Hz), 2.47 (2H, t, J=8Hz), 2.10-1.92 (2H, m).

Reference example 2

Methyl 3-(4-hydroxyheptyl)phenoxyacetate



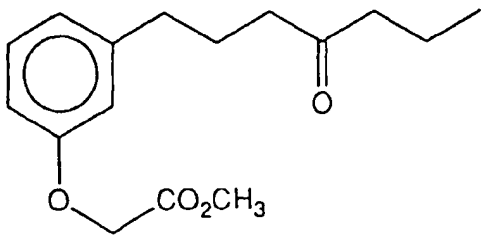
To a solution of the compound prepared in reference example 1 (1.26 g) in diethyl ether (10 ml), n-propylmagnesium bromide (3.0 ml of 2M in diethyl ether) was added dropwise at -70°C. The reaction mixture was stirred for 2h with warming still -30 °C. After quenched by addition of a saturated aqueous solution of ammonium chloride, the mixture was extracted with ether. The extract was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 2 : 1) to give the title compound (820 mg) having the following physical data.

TLC: Rf 0.23 (n-hexane : ethyl acetate = 2 : 1);

NMR: δ 7.36-7.08 (1H, m), 6.95-6.60 (3H, m), 4.64 (2H, s), 3.82 (3H, s), 3.80-3.50 (1H, m), 2.80-2.36 (3H, m), 2.20-1.25 (8H, m), 1.10-0.80 (3H, m).

Reference example 3

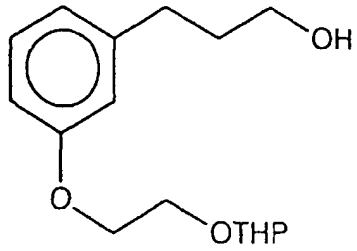
Methyl 3-(4-oxoheptyl)phenoxyacetate



Pyridium dichromate (2.53 g) was added to a solution of the compound prepared in reference example 2 (750 mg) in dimethylformamide (10 ml) at room temperature. The mixture was stirred overnight. Celite (registerd trade mark) and florisil (registerd trade mark) were added to the mixture. The mixture was diluted with a mixture of n-hexane-ethyl acetate (3:1)(20 ml). The mixture was filtered through florisil, the filtrate was evaporated. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 5 : 1) to give the title compound (350 mg) having the following physical data.
TLC: Rf 0.30 (n-hexane : ethyl acetate = 3 : 1);
NMR: δ 7.36-7.08 (1H, m), 6.90-6.60 (3H, m), 4.62 (2H, s), 3.81 (3H, s), 2.72-2.25 (6H, m), 2.10-1.38 (4H, m), 0.90 (3H, t, J=8Hz).

Reference example 4

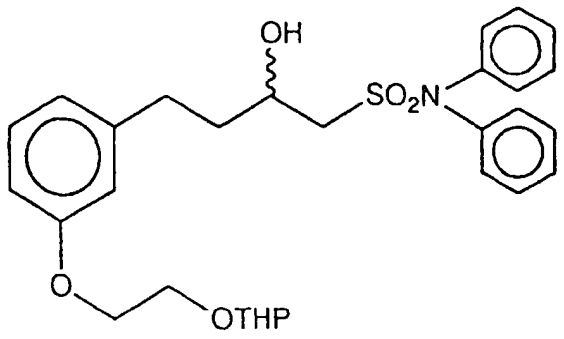
3-[3-[2-(tetrahydropyran-2-yl)oxyethoxy]phenyl]propanol



To a suspension of sodium hydride (1.84 g, 60% dispersion) in dimethylformamide (50 ml) was added dropwise a solution of 3-(3-hydroxypropyl)phenol (7.0 g) in dimethylformamide (20 ml) at 0 °C. The mixture was stirred for 1 h at room temperature. To the reaction mixture, was added 1-bromo-2-(tetrahydropyran-2-yl)ethane (5.46 g) at 0 °C. The mixture was stirred for 1 h at room temperature. After quenched by addition of water and the mixture was extracted with ether. The extract was washed with 2N aqueous solution of sodium hydroxide, water and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 2 → 2 : 1) to give the title compound (3.36 g) having the following physical data.
TLC: Rf 0.17 (ethyl acetate : n-hexane = 1 : 2);
IR(cm^{-1}): ν 3369, 2930, 1584, 1488, 1451, 1384, 1353, 1260, 1202, 1125, 1034, 992, 874, 814, 777, 695.

Reference example 5

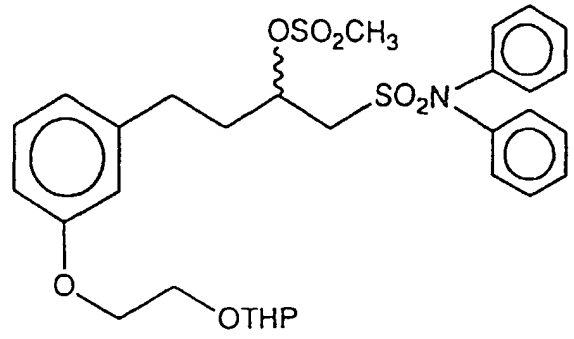
1-[2-(Tetrahydropyran-2-yl)oxyethoxy]-3-(3-hydroxy-4-diphenylamino sulfonylbutyl)benzene



To a solution of N,N-diphenylsulfonamide (0.99 g) in a mixture of tetrahydrofuran-hexamethylphosphoramide (20: 3) (23 ml) was added dropwise n-butyllithium (3.75 ml of 1.6 M in n-hexane) at -78 °C. The mixture was stirred for 30 min at -78 °C. To the mixture obtained was added a solution of a compound (which was prepared by the same procedure as reference example 1, using the compound prepared in reference example 4) (1.11 g) in tetrahydrofuran (10 ml). The reaction mixture was stirred for 1h at -78 °C. After quenched by addition of water and the mixture was extracted with ethyl acetate. The extract was washed with water, and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 2) to give the title compound (0.84 g) having the following physical data.
TLC: Rf 0.37 (ethyl acetate : benzene = 1 : 1);
IR(cm^{-1}): ν 3401, 3063, 2930, 1586, 1489, 1451, 1351, 1261, 1190, 1150, 1077, 1050, 1011, 969, 903, 822, 757, 697.

Reference example 6

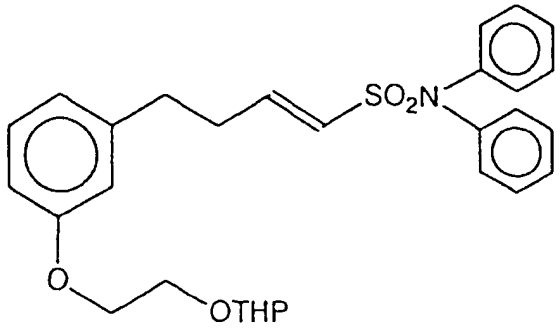
1-[2-(Tetrahydropyran-2-yl)oxyethoxy]-3-(3-methylsulfonyloxy-4-diphenylaminosulfonylbutyl)benzene



To a solution of the compound prepared in reference example 5 (0.66 g) in methylene chloride (20 ml) were added successively triethylamine (0.305 g) and methanesulfonyl chloride (0.12 ml) at 0 °C. The mixture was stirred for 10 min at same temperature. After quenched by addition of water and the mixture was extracted with ethyl acetate. The extract was washed with a saturated aqueous solution of ammonium chloride, water and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated. The residue containing the title compound having the following physical data. The residue was used for the next reaction without further purification.
TLC: Rf 0.31 (ethyl acetate : benzene = 1 : 8).

Reference example 7

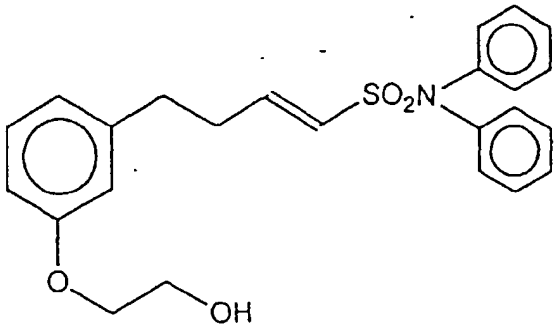
1-[2-(Tetrahydropyran-2-yl)oxyethoxy]-3-(4-diphenylaminosulfonyl-3-butenyl)benzene



To a solution of the residue obtained in reference example 6 in benzene was added 1, 8-diazabicyclo[5, 4, 0]-7-undecene (0.382 g) at 0 °C. The mixture was stirred for 10 min at 0 °C. After quenched by addition of water and the mixture was extracted with ethyl acetate. The extract was washed with a saturated aqueous solution of ammonium chloride, water and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated to give the title compound (0.63 g) having the following physical data.
TLC: Rf 0.27 (ethyl acetate : benzene = 1 : 8);
IR (cm^{-1}): ν 3063, 2943, 2873, 1734, 1586, 1489, 1451, 1354, 1260, 1152, 1126, 1076, 1034, 989, 969, 904, 874, 816, 757, 697.

Reference example 8

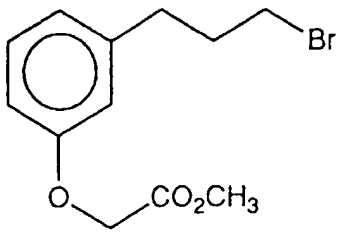
2-[3-(4-Diphenylaminosufonyl-3-butenyl)phenoxy]ethanol



To a solution of the compound prepared in reference example 7 (0.541 g) in methanol (20 ml) was added a catalytic amount of 10-camphorsulfonic acid (dl form) at room temperature. The mixture was stirred for 1h at room temperature. To the reaction mixture was added triethylamine (0.1 ml) and evaporated. The residue was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 2 → 1 : 1) to give the title compound (0.404 g) having the following physical data.
TLC: Rf 0.37 (ethyl acetate : benzene = 1 : 1);
IR(cm^{-1}): ν 3401, 3063, 2930, 1586, 1489, 1451, 1351, 1261, 1190, 1150, 1077, 1050, 1011, 969, 903, 822, 757, 697.

Reference example 9

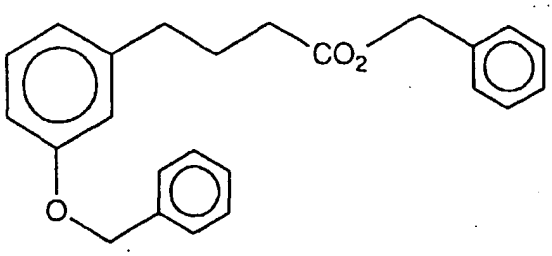
Methyl 3-(3-bromopropyl)phenoxyacetate



To a stirred solution of methyl 3-(3-hydroxypropyl)phenoxyacetate (2.00 g) in methylene chloride (20 ml) were added successively triphenylphosphine (2.81 g) and tetrabromomethane (3.55 g) at room temperature. The mixture was evaporated. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 7 : 1) to give the title compound (1.69 g) having the following physical data.
TLC: Rf 0.26 (n-hexane : ethyl acetate = 2 : 1);
NMR: δ 7.30-7.06 (1H, m), 6.90-6.60 (3H, m), 4.63 (2H, s), 3.81 (3H, s), 3.38 (2H, t, J=8Hz), 2.76 (2H, t, J=8Hz), 2.32-1.96 (2H, m).

Reference example 10

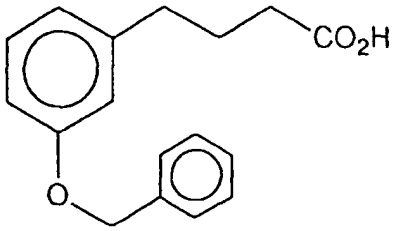
1-Benzyloxy-3-(3-benzyloxycarbonylpropyl)benzene



A mixture of 1-hydroxy-3-(3-benzyloxycarbonylpropyl)benzene (2.0 g), benzylbromide (1.14 ml), potassium bicabonate (1.53 g) and dimethylformamide (20 ml) was stirred for 3h at room temperature. The mixture was quenched by addition of water and extracted with a mixture of n-hexane : ethyl acetate (3 : 1). The extract was washed with water and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 10 : 1) to give the title compound (2.55 g) having the following physical data.
TLC: Rf 0.33 (n-hexane : ethyl acetate = 7 : 1);
IR(cm^{-1}): ν 3065, 3033, 2939, 2866, 1734, 1583, 1489, 1455, 1382, 1315, 1258, 1156, 1082, 1027, 908, 850, 777, 739.

Reference example 11

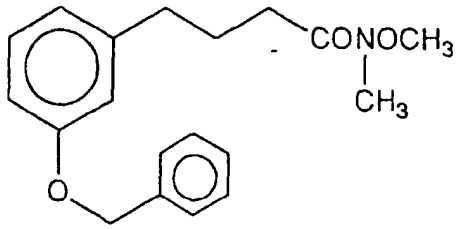
4-(3-Benzyloxyphenyl)butanoic acid



To a solution of the compound prepared in reference example 10 (2.42 g) in a mixture of tetrahydrofuran-methanol (2 : 1) (20 ml) was added 2N aqueous solution of sodium hydroxide (11 ml) at 0 °C. The mixture was stirred for 3h at room temperature. After neutralized by addition of 2N aqueous solution of hydrochloric acid and the mixture was extracted with ethyl acetate. The extract was washed with water and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated. The residue was recrystallized from n-hexane-ethyl acetate to give the title compound (1.5 g) having the following physical data.
mp.: 100.0-102.0 °C;
TLC: Rf 0.53 (ethyl acetate);
NMR: δ 7.50-7.08 (7H, m), 6.93-6.70 (3H, m), 5.04 (2H, s), 2.66 (2H, t, J=7Hz), 2.36 (2H, t, J=8Hz), 2.16-1.93 (2H, m).

Reference example 12

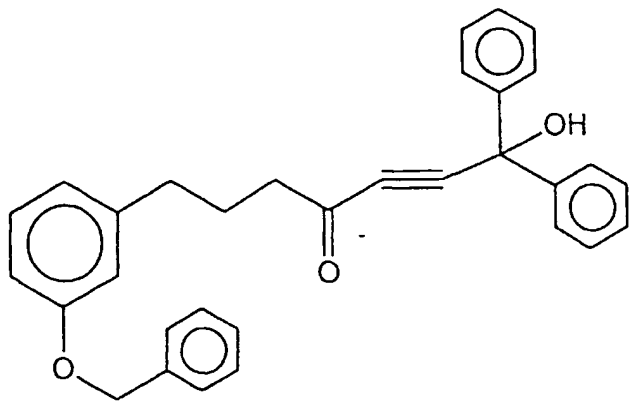
1-Benzyloxy-3-[3-(N-methyl-N-methoxyamino)carbonylpropyl]benzene



An ethyl chloroformate (0.96 ml) was dissolved with stirring solution of a compound prepared in reference example 11 (2.45 g) and triethylamine (1.35 ml) in methylene chloride (30 ml) at -10 °C. After stirred for 10 min at room temperature, to the mixture were added successively triethylamine (2.8 ml) and N-methyl-N-methoxyamine hydrochloride (980 mg) at -10 °C. The mixture was further stirred for 1h at room temperature, and was poured into water. The mixture was extracted with a mixture of n-hexane-ethyl acetate (1 : 1). The extract was washed with water and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 2 : 1) to give the title compound (2.67 g) having the following physical data.
TLC: Rf 0.23 (n-hexane : ethyl acetate = 2 : 1);
NMR: δ 7.48-7.03 (6H, m), 6.86-6.67 (3H, m), 5.04 (2H, s), 3.61 (3H, s), 3.16 (3H, s), 2.78-2.30 (4H, m), 2.12-1.80 (2H, m).

Reference example 13

1-Benzyloxy-3-(3-hydroxy-3,3-diphenyl-1-propynyl)carbonylpropyl benzene

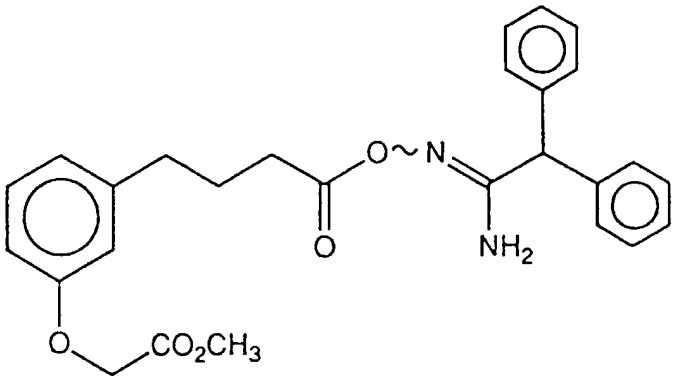


To a solution 1,1-diphenyl-2-propyn-1-ol (3.89 g) in tetrahydrofuran (40 ml) was added n-butyllithium (23.4 ml of 1.6M in n-hexane) at -78 °C. After stirred for 30 min at same temperature, to the mixture was added boron trifluoride

etherate (5.05 ml). The mixture was stirred for 30 min at -78 °C. To the mixture, the compound prepared in reference example 12 (2.67 g) in tetrahydrofuran (20 ml) was added at same temperature. After stirred for 1h at -78 °C, the reaction mixture was quenched by addition of a saturated aqueous solution of ammonium chloride, and the mixture stirred for 30 min at room temperature. The mixture was extracted with a mixture of n-hexane-ethyl acetate (3 : 1). The extract was washed with water and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 7 : 1) to give the title compound (2.8 g) having the following physical data.
mp.: 54.5 - 56.0 °C
TLC: Rf 0.18 (n-hexane : ethyl acetate = 6 : 1);
NMR: δ 7.45-7.10 (16H, m), 6.86-6.71 (3H, m), 5.01 (2H, s), 3.00 (1H, s), 2.68-2.53 (4H, m), 2.10-1.90 (2H, m).

Reference example 17

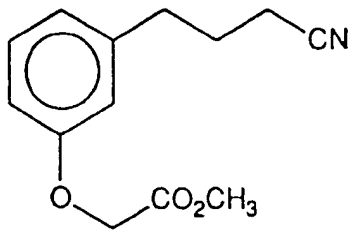
Methyl 3-[3-[(1-amino-2, 2-diphenylethylidene)aminooxycarbonyl] propyl]phenoxyacetate



A suspension of 4-(3-methoxycarbonylmethoxyphenyl)butanoic acid (289 mg) and thionyl chloride (5.0 ml) was refluxed for 1 h. The mixture was cooled to room temperature and concentrated under reduced pressure. To a suspension of the reside and 1,1-diphenyl-2-amino-2-hydroxyiminoethane (285 mg) in methylene chloride (5 ml) was added tiethylamine (0.32 ml) with stirring at room temperature. The mixture was stirred overnight at room temperature. After quenched by addition of water, the mixture was extracted with ether. The extract was washed with water and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated. The reside was purified by silica gel flash chromatography (n-hexane : ethyl acetate = 1 : 1) to give the title compound (193 mg) having the following physical data.
NMR: δ 7.40-7.00 (11H, m), 6.90-6.50 (3H, m), 5.26 (1H, s), 4.75 (2H, brs), 4.58 (2H, s), 3.78 (3H, s), 2.64 (2H, t, J=7Hz), 2.40 (2H, t, J=7Hz), 2.00 (2H, m); MS (m/z): 461 (M^++1).

Reference example 18

Methyl 3-(3-cyanopropyl)phenoxyacetate

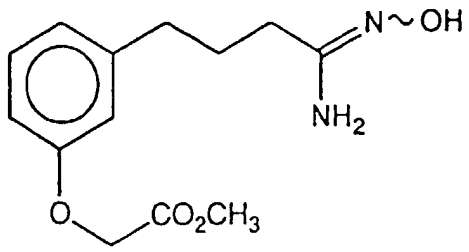


A mixture of potassium cyanide (1.16 g), 18-crown-6 (236 mg) and acetonitrile (18 ml) was stirred for 15 min under

an atmosphere of argon. A mixture of methyl 3-(3-hydroxypropyl)phenoxyacetate (2.0 g) and tributylphosphine (1.99 g) in acetonitrile (10 ml) was added to the reaction mixture, followed by the dropwise addition of a solution of carbon tetrachloride (0.95 ml) in acetonitrile (10 ml) with cooling in ice bath. The mixture was stirred overnight at room temperature. The mixture was diluted with ether, and washed with aqueous 10% citric acid. After the addition of carbon tetrachloride (10 ml), the mixture was washed with water and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated. The reside was purified by silica gel column chromatography (ethyl acetate : n-hexane = 9 : 1) to give the title compound (1.47 g) having the following physical data. NMR: δ 7.20 (1H, t, J=7Hz), 6.90-6.60 (3H, m), 4.60 (2H, s), 3.80 (3H, s), 2.74 (2H, t, J=7Hz), 2.30(2H, t, J=7 Hz), 1 . 98(2H, m).

Reference example 19

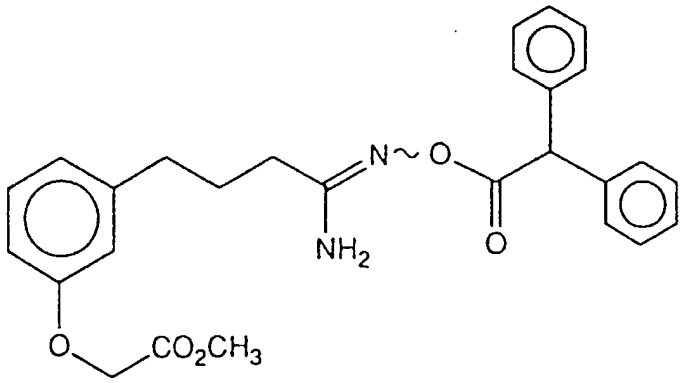
Methyl 3-(4-amino-4-hydroxyiminobutyl)phenoxyacetate



To a mixture of ethanol-water (5:1) (30 ml) were added successively the compound prepared in reference example 18 (1.01 g), hydroxyamine hydrochloride (331 mg) and sodium acetate (391 mg). The mixture was refluxed overnight. The mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 1 : 1) to give the title compound (150 mg) having the following physical data.
NMR: δ 7.13 (1H, t, J=7 Hz), 6.90-6.50 (3H, m), 5.10 (3H, brs), 4.60 (2H, s), 3.80 (3H, s), 2.63 (2H, t, J= 7 Hz), 2.37 (2H, t, J=7 Hz), 1.95 (2H, m).

Reference example 20

Methyl 3-(4-amino-4-diphenylmethylcarbonyloxyiminobutyl)phenoxy acetate

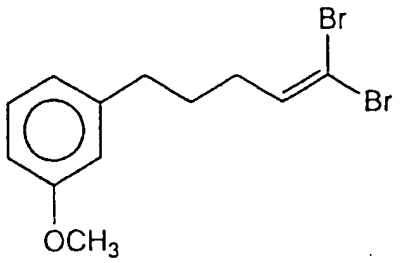


A suspension of diphenylacetic acid (252 mg) and thionyl chloride (5.0 ml) was refluxed for 1h. The mixture was cooled to room temperature and concentrated under reduced pressure. To a solution of the residue and the compound prepared in reference example 19 (144 mg) in methylene chloride (5.0 ml) was added triethylamine (0.33 ml) at room temperature. The mixture was stirred overnight at room temperature, quenched by addition of water, and extracted with ether. The extract was washed with water and a saturated aqueous solution of sodium chloride, successively,

dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel flash chromatography (n-hexane : ethyl acetate = 1 : 1) to give the title compound (61 mg) having the following physical data.
NMR: δ 7.40-7.00 (11H, m), 6.90-6.50 (3H, m), 5.10 (1H, s), 4.58 (2H, s), 3.79 (3H, s), 2.60 (2H, m), 2.21 (2H, m), 1.90 (2H, m);
MS (m/z): 461 (M^++1).

Reference example 21

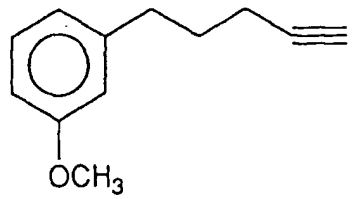
1-(5,5-Dibromo-4-pentenyl)-3-methoxybenzene



To a solution of carbon tetrabromide (16.7 g) in methylene chloride (35 ml) was added triphenylphosphine (26.0 g) in methylene chloride (35 ml) at 0°C, and the mixture was stirred for 10 min. To the mixture was added a solution of 1-(3-formylpropyl)-3-methoxybenzene (3.00 g) in methylene chloride (20 ml) at 0°C. The mixture was stirred for 30 min at 0°C. To the mixture was gradually added n-hexane, and filtrated to remove triphenylphosphineoxide. The filtrate was washed with water and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 24 : 1) to give the title compound (5.33 g) having the following physical data.
MS (m/z): 334 (M^+).
TLC: Rf 0.34 (n-hexane : ethyl acetate = 24 : 1).

Reference example 22

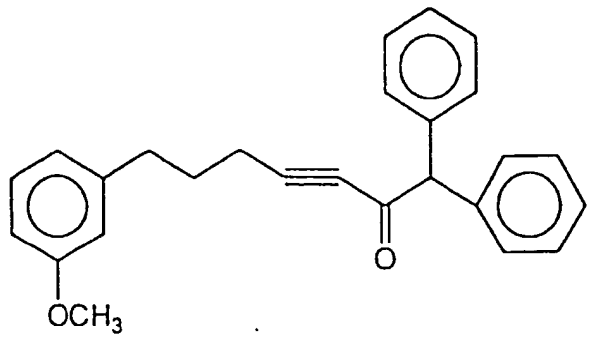
1-(4-pentynyl)-3-methoxybenzene



To a solution of the compound prepared in reference example 21 (3.58 g) in THF (40 ml) was added dropwise n-butyllithium (14.7 ml; 1.6M/L in hexane solution) at -70°C. The mixture was stirred for 30 min at -70°C. After quenched by addition of water and aqueous solution of ammonium chloride at the same temperature, the mixture was warmed up to room temperature. The mixture was extracted with n-hexane - ethyl acetate (6 : 1). The extract was washed with water and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 24 : 1) to give the title compound (1.86 g) having the following physical data.
TLC: Rf 0.32 (n-hexane : ethyl acetate = 24 : 1);
IR(cm^{-1}): ν 3295, 2943, 2117, 1602, 1489, 1261.

Reference example 23

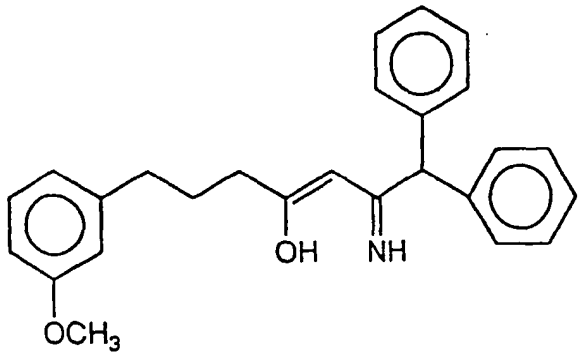
1-(7,7-Diphenyl-6-oxo-4-heptynyl)-3-methoxybenzene



To a mixture of ethylmagnesium bromide (3.4 ml; 3.0 M/L in ether solution) and THF (20 ml) was added dropwise a solution of the compound prepared in reference example 22 (1.5 g) in THF (15 ml) over a 10 min period. The mixture was stirred for 2h at room temperature. To the mixture was added a solution of diphenylacetaldehyde (1.7 g) in THF (10 ml). The mixture was stirred for 2h. After quenched by addition of ammonium chloride, the mixture was extracted with ether. The extract was washed with water and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated. To a solution of the residue in ether (40 ml) was added manganese (IV) oxide (2.0 g) at room temperature. The mixture was stirred for 2h. The mixture was filtrated, and evaporated. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 7 : 1) to give the title compound (1.99 g) having the following physical data.
MS (m/z): 368 (M^+).
TLC: Rf 0.46 (n-hexane : ethyl acetate = 3 : 1).

Reference example 24

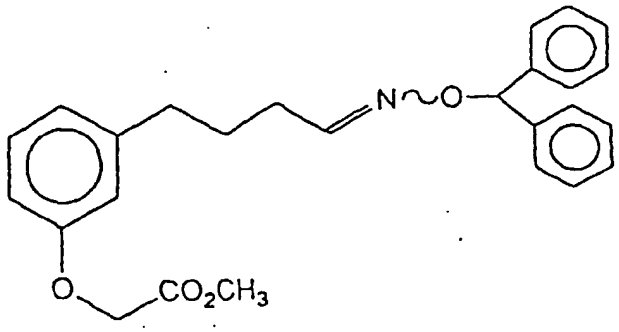
1-(6-Imino-4-hydroxy-7,7-diphenyl-4-heptynyl)-3-methoxybenzene



A mixture of the compound (400 mg) prepared by the same procedure as reference example 14 using the compound prepared in reference example 23, Raney nickel (300 mg; registered trade mark) and ethanol (5 ml) was stirred overnight under an atmosphere of hydrogen. The mixture was filtered through Celite (registered trade mark), and evaporated. The residue was purified by silica gel column chromatography (ethyl acetate : benzene = 7 : 93) to give the title compound (184 mg) having the following physical data. MS (m/z): 385 (M+).
TLC: Rf 0.26 (n-hexane : ethyl acetate = 3 : 1).

Example 1

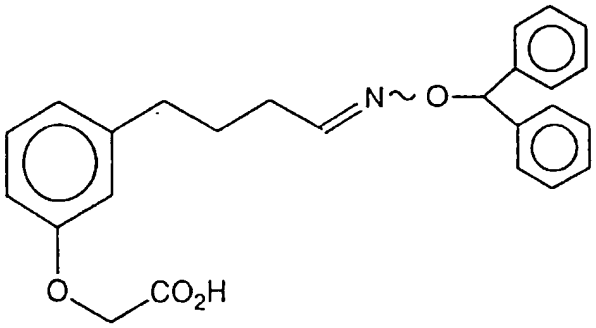
Methyl 3-(4-diphenylmethyloxyiminobutyl)phenoxyacetate



To a solution of the compound prepared in reference example 1 (300 mg) in ethanol (10 ml) was added diphenylmethyloxyamine (253 mg) at room temperature. The mixture was stirred overnight at room temperature and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (benzene : ethyl acetate = 9 : 1) to give the title compound (520 mg) having the following physical data.
TLC: Rf 0.31 (n-hexane : ethyl acetate = 4 : 1);
NMR: δ 7.60-7.10 (12H, m), 6.90-6.80 (3H, m), 6.22 (1H, s), 4.60 (2H, s), 3.79 (3H, s), 2.80-2.00 (4H, m), 1.80 (2H, m).

Example 2

3-(4-Diphenylmethyloxyiminobutyl)phenoxyacetic acid

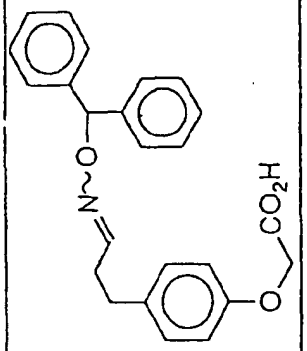
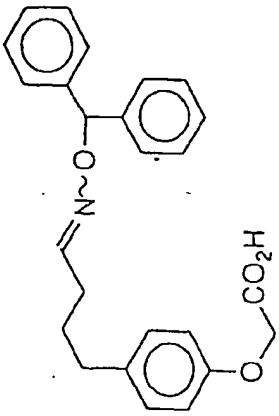
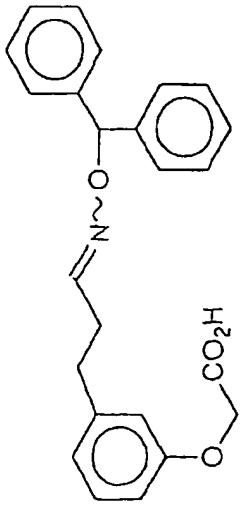


To a solution of the compound prepared in example 1 (305 mg) in a mixture of dimethoxymethane (3.0 ml) and methanol (1.0 ml) was added 2N aqueous solution of sodium hydroxide (0.5 ml) at room temperature. After stirred for 1h, the mixture was quenched by addition of 1N hydrochloric acid (0.5 ml), and extracted with ethyl acetate. The extract was washed with water and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 1) to give the title compound (277 mg) having the following physical data.
MS (m/z): 403 (M^+), 381, 359, 345, 236, 219, 184, 168;
NMR: δ 7.55 (1H, t, J=6 Hz), 7.40-7.10 (11H, m), 6.90-6.80 (3H, m), 6.20 (1H, s), 4.62 (2H, s), 2.80-2.40 (3H, m), 2.17 (1H, brs), 1.80 (2H, m).

Example 2(a)-2(c)

By the same procedure as in example 2, using the compound prepared in the same procedure as in reference example 1 → example 1 which was using corresponding phenoxyacetic acid derivative compound instead of methyl 3-(4-hydroxybutyl) phenoxyacetate, compounds having the following physical data shown in the table 3 were given.

Table 3

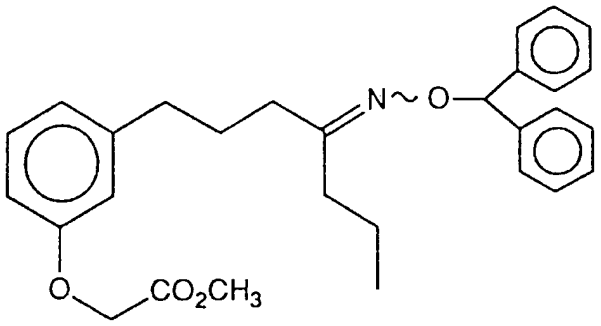
Ex. No.	Structure of the example compound	MS (m/z)	IR (cm^{-1})
2 (a)		389(M^+), 344. 222. 205. 184. 168	[KBr method] ν 3030. 2911. 1743. 1708. 1610. 1515. 1455. 1431. 1237. 1189. 1095. 1023. 919. 832. 746. 705
2 (b)		403(M^+), 360. 345. 236. 219. 184. 118. 152	ν 3030. 2927. 1736. 1611. 1586. 1510. 1454. 1301. 1218. 1180. 1081. 1022. 920. 830. 740. 702. 609
2 (c)		390 (M^+ + 1)	ν 3031. 2922. 1734. 1586. 1494. 1454. 1241. 1160. 1084. 1020. 919. 746. 700

The example compounds shown in the table 3 are named as follows:

2(a) 4-(3-Diphenylmethyloxyiminopropyl)phenoxyacetic acid,
2(b) 4-(4-Diphenylmethyloxyiminobutyl)phenoxyacetic acid,
2(c) 3-(3-Diphenylmethyloxyiminopropyl)phenoxyacetic acid,

Example 3

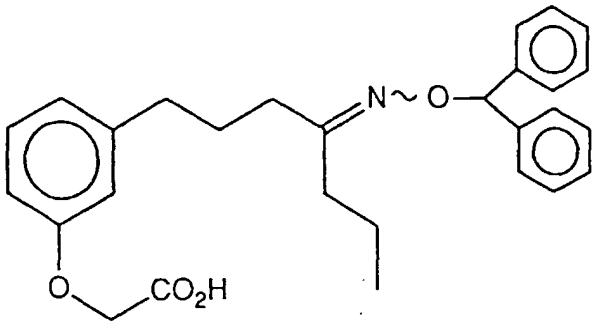
Methyl 3-(4-diphenylmethyloxyiminoheptyl)phenoxyacetate



By the same procedure as in example 1, using the compound prepared in reference example 3, the title compound having the following physical data was given.
TLC: Rf 0.35 (n-hexane : ethyl acetate = 3 : 1);
IR (cm^{-1}): ν 3062, 3030, 2958, 2872, 1763, 1741, 1586, 1494, 1452, 1377, 1289, 1209, 1159, 1088, 1025, 937, 744, 700.

Example 4

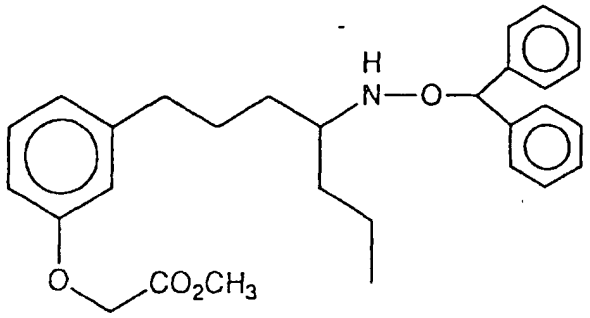
3-(4-Diphenylmethyloxyiminoheptyl)phenoxyacetic acid



By the same procedure as in example 2, using the compound prepared in example 3, the title compound having the following physical data was given.
TLC: Rf 0.20 (chloroform : methanol = 4 : 1);
IR (cm^{-1}): ν 3031, 2961, 2872, 1737, 1587, 1494, 1454, 1375, 1241, 1160, 1086, 1042, 938, 763, 744, 700.

Example 5

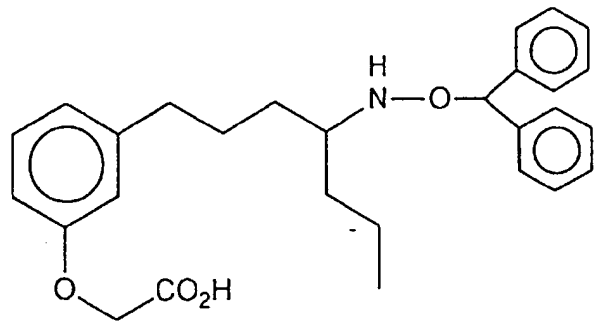
Methyl 3-(4-diphenylmethyloxyaminoheptyl)phenoxyacetate



To a solution of the compound prepared in example 3 (150 mg) in methanol (1 ml) was added sodium cyanoborohydride (82 mg) at room temperature. This solution was adjusted to pH 3 by addition of a saturated hydrochloride in methanol and this mixture was stirred for 2h at room temperature. After neutralized by addition of a saturated aqueous solution of sodium bicarbonate, the mixture was extracted with ethyl acetate. The extract was washed with water and aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 3 : 1) to give title compound (147 mg) having the following physical data.
TLC: Rf 0.34 (n-hexane : ethyl acetate = 3 : 1);
IR (cm^{-1}): ν 3030, 2932, 2869, 1764, 1741, 1586, 1493, 1452, 1376, 1209, 1159, 1086, 1029, 888, 761, 743, 699.

Example 6

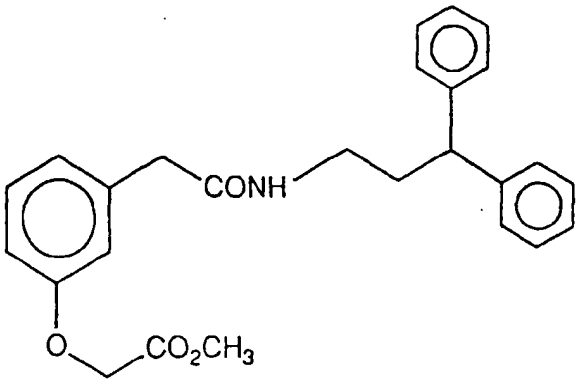
3-(4-Diphenylmethyloxyaminoheptyl)phenoxyacetic acid



By the same procedure as example 2, using the compound prepared in example 5 (125 mg), the title compound (115 mg) having the following physical data was given.
TLC: Rf 0.21 (chloroform : methanol = 4 : 1);
IR (cm^{-1}): ν 3031, 2932, 2871, 1738, 1586, 1494, 1454, 1374, 1241, 1159, 1082, 1046, 915, 762, 744, 698.

Example 7

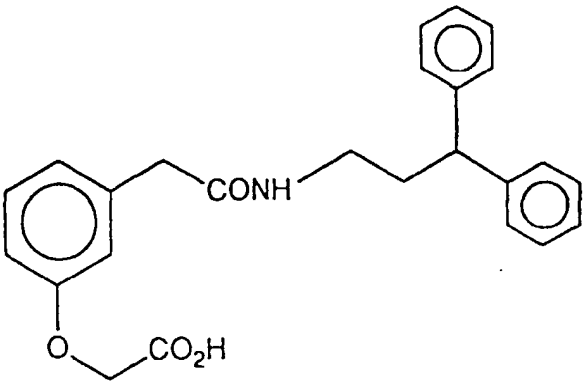
Methyl 3-(3,3-diphenylmethylpropyl)aminocarbonylmethyl)phenoxy acetate



A mixture of 3-methoxycarbonylmethoxyphenylacetic acid (150 mg), 2-chloro-N-methylpyridinium iodide (241 mg), 3,3-diphenylpropylamine (146 mg) and triethylamine (0.26 ml) in methylene chloride (7 ml) was stirred overnight at room temperature. The mixture was poured into 1N hydrochloric acid, and extracted with ether. The extract was washed with water and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (ethyl acetate : methylene chloride = 1 : 25) to give title compound (125 mg) having the following physical data.
TLC: Rf 0.33 (ethyl acetate : methylene chloride = 1 : 9);
NMR: δ 7.40-7.00 (11H, m), 6.90-6.70 (3H, m), 5.30 (1H, m), 4.63 (2H, s), 3.83 (1H, t, J=7Hz), 3.80 (3H, s), 3.47 (2H, s), 3.17 (2H, dt, J=8, 7Hz), 2.20 (2H, dt, J=5, 7Hz).

Example 8

3-(3,3-diphenylpropyl)aminocarbonylmethyl)phenoxyacetic acid



By the same procedure as example 2, using the compound prepared in example 7 (119 mg), the title compound (98 mg) having the following physical data was given.
TLC: Rf 0.48 (methylene chloride : methanol = 10 : 3);
IR (cm^{-1}): ν 3295, 3024, 2880, 2526, 1757, 1584, 1557, 1490, 1469, 1450, 1381, 1356, 1304, 1285, 1242, 1204, 1155, 1087, 1030, 958, 905, 880, 776, 753, 741, 697, 674, 638, 614, 588, 557, 482, 456, 431.

Example 8(a) - 8(cc)

By the same procedure as in example 7 → example 2, using corresponding phenoxyacetic acid derivative compound and corresponding amine, compounds having the following physical data shown in the table 4 were given.

Table 4

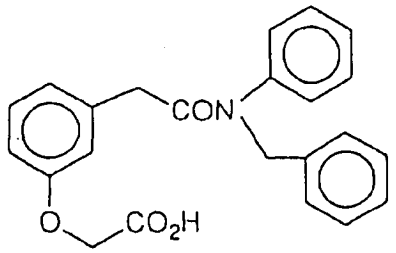
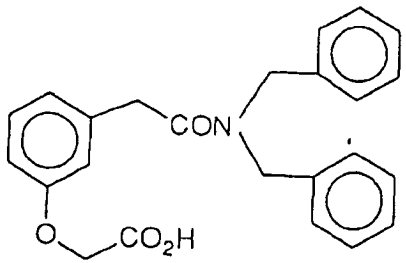
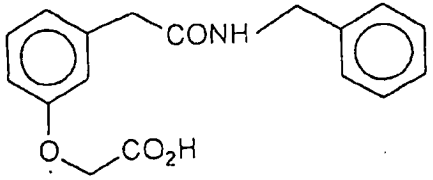
EX. No.	Structure of the example compound	TLC	IR (cm^{-1})
8 (a)		Rf 0.50 (methylene chloride : methanol = 10:3)	ν 3033. 1742. 1614. 1587. 1495. 1438. 1213. 1159. 1062. 1017. 780. 732. 702
8 (b)		Rf 0.53 (methylene chloride : methanol = 10:3)	ν 3436. 3031. 1742. 1603. 1494. 1452. 1363. 1221. 1160. 1083. 1029. 954. 775. 736. 700
8 (c)		Rf 0.30 (methylene chloride : methanol = 10:3)	[KBr method] ν 3268. 3057. 1724. 1636. 1588. 1561. 1492. 1453. 1432. 1400. 1368. 1348. 1314. 1283. 1259. 1231. 1172. 1158. 1093. 1080. 1026. 951. 919. 855. 787. 766. 744. 698. 618. 605. 557. 532. 489

Table 4 (continued)

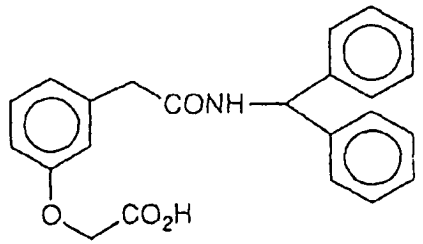
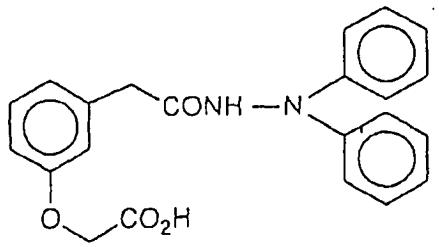
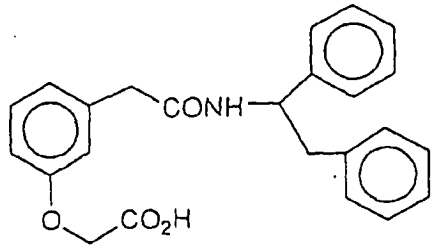
EX. No.	Structure of the example compound	TLC	IR (cm^{-1})
8 (d)		Rf 0.40 (methylene chloride : methanol = 10:3)	[KBr method] ν 3297. 3058. 2917. 1719. 1703. 1653. 1613. 1589. 1531. 1494. 1451. 1434. 1412. 1359. 1341. 1277. 1237. 1161. 1085. 1032. 978. 752. 742. 702. 642. 620.
8 (e)		Rf 0.40 (methylene chloride : methanol = 10:3)	[KBr method] ν 3273. 3038. 2916. 1753. 1674. 1590. 1516. 1494. 1460. 1431. 1315. 1276. 1241. 1163. 1098. 1085. 1030. 965. 877. 784. 752. 693. 626. 546. 507
8 (f)		Rf 0.40 (methylene chloride : methanol = 10:3)	[KBr method] ν 3318. 3063. 2921. 1752. 1646. 1586. 1540. 1495. 1440. 1255. 1165. 1100. 1028. 936. 914. 877. 760. 701. 541

Table 4 (continued)

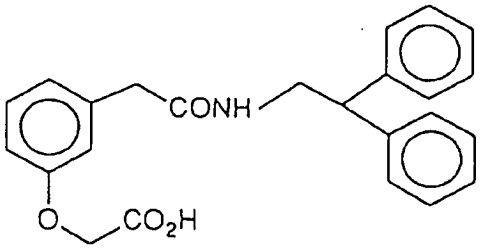
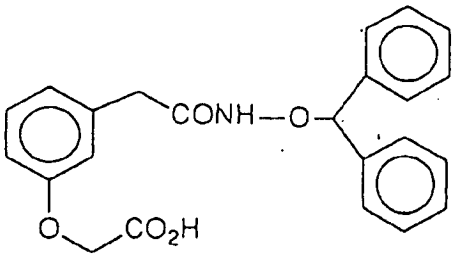
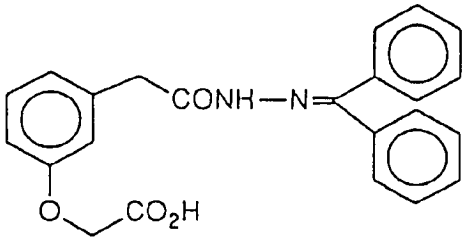
EX. No.	Structure of the example compound	TLC	IR (cm^{-1})
8 (g)		Rf 0.40 (methylene chloride : methanol = 10:3)	[KBr method] ν 3309. 3028. 2912. 1724. 1625. 1604. 1580. 1494. 1435. 1299. 1246. 1160. 1087. 1013. 924. 886. 774. 756. 742. 704. 633. 585. 542
8 (h)		Rf 0.38 (methylene chloride : methanol = 10:3)	[KBr method] ν 3233. 3032. 2912. 1719. 1641. 1609. 1588. 1532. 1494. 1458. 1436. 1341. 1300. 1250. 1161. 1098. 1086. 1054. 985. 914. 888. 813. 764. 748. 698. 602. 574. 531
8 (i)		Rf 0.40 (methylene chloride : methanol = 10:3)	[KBr method] ν 3314. 3057. 1737. 1639. 1587. 1511. 1490. 1446. 1367. 1324. 1304. 1221. 1158. 1075 1028. 1000. 972. 918. 879. 774. 695. 651. 628. 549. 452

Table 4 (continued)

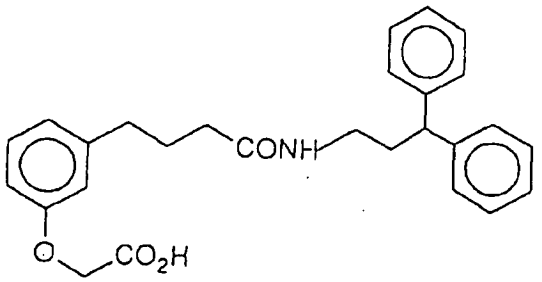
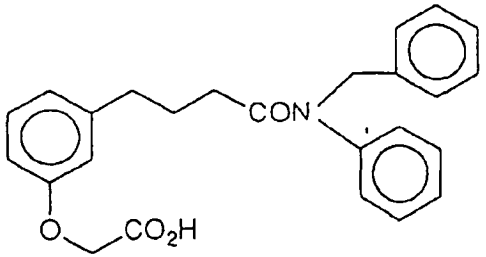
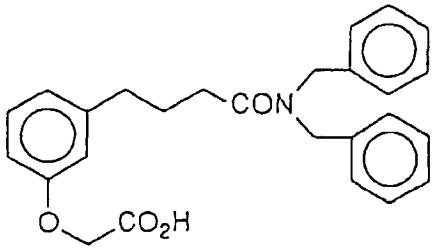
EX. No.	Structure of the example compound	TLC	IR (cm^{-1})
8 (j)		Rf 0.50 (methylene chloride : methanol = 10:3)	ν 3351. 3027. 2933. 1734. 1713. 1603. 1558. 1494. 1452. 1364. 1227. 1160. 1089. 1031. 914. 770. 752. 701
8 (k)		Rf 0.53 (methylene chloride : methanol = 10:3)	ν 3033. 2930. 1742. 1611. 1586. 1495. 1453. 1413. 1357. 1267. 1208. 1158. 1079. 1017. 878. 777. 700
8 (l)		Rf 0.53 (methylene chloride : methanol = 10:3)	ν 3031. 2927. 1746. 1604. 1495. 1452. 1364. 1223. 1160. 1083. 1029. 953. 879. 783. 735. 699

Table 4 (continued)

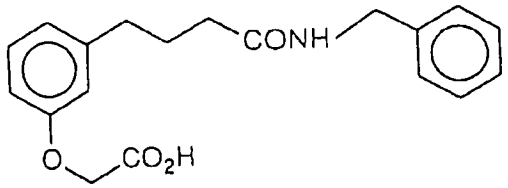
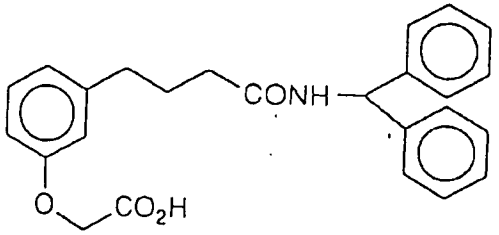
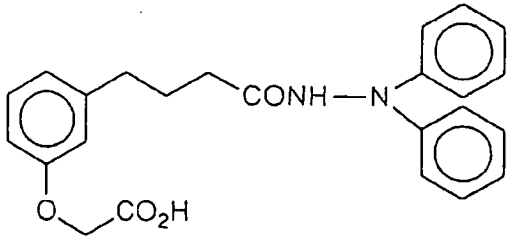
EX. No.	Structure of the example compound	TLC	IR (cm^{-1})
8 (m)		Rf 0.33 (methylene chloride : methanol = 10:3)	[KBr method] ν 3320. 3031. 2952. 2587. 1737. 1641. 1611. 1580. 1541. 1485. 1461. 1423. 1377. 1349. 1297. 1279. 1239. 1165. 1103. 1030. 1009. 925. 877. 781. 770. 735. 695
8 (n)		Rf 0.50 (methylene chloride : methanol = 10:3)	[KBr method] ν 3320. 3034. 2948. 1750. 1644. 1586. 1532. 1495. 1459. 1426. 1377. 1304. 1258. 1243. 1212. 1164. 1100. 1032. 935. 873. 756. 698. 644. 605
8 (o)		Rf 0.56 (methylene chloride : methanol = 10:3)	[KBr method] ν 3279. 3027. 2932. 2587. 1744. 1669. 1591. 1518. 1495. 1430. 1383. 1329. 1256. 1206. 1174. 1094. 1031. 939. 923. 853. 782. 746. 698. 631. 559

Table 4 (continued)

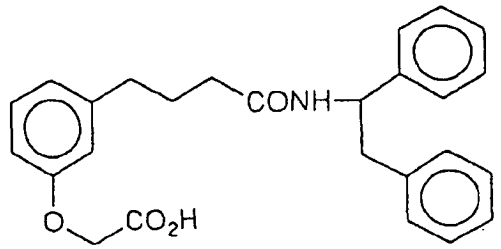
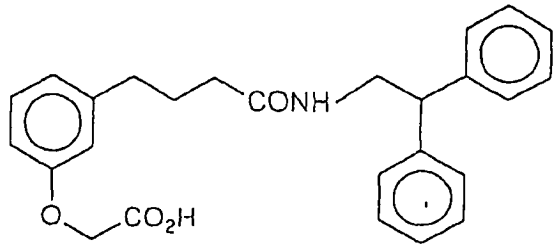
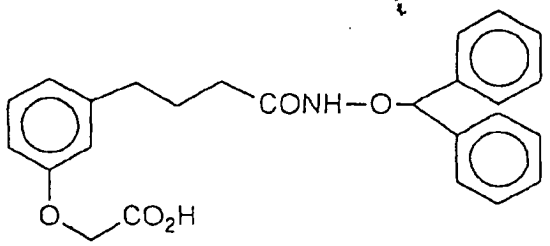
EX. No.	Structure of the example compound	TLC	IR (cm^{-1})
8 (p)		Rf 0.45 (methylene chloride : methanol = 10:3)	[KBr method] ν 3344. 3031. 2944. 1746. 1640. 1603. 1523. 1495. 1454. 1419. 1244. 1168. 1090. 1031. 902. 785. 781. 702. 642. 584. 538
8 (q)		Rf 0.47 (methylene chloride : methanol = 10:3)	[KBr method] ν 3347. 2938. 2866. 2549. 1737. 1615. 1587. 1553. 1493. 1452. 1437. 1362. 1293. 1226. 1158. 1083. 1028. 908. 877. 790. 759 704. 630. 587. 543
8 (r)		Rf 0.44 (methylene chloride : methanol = 10:3)	[KBr method] ν 3205. 2930. 1736. 1655. 1586. 1494. 1452. 1229. 1160. 1082. 1023. 875. 762. 746. 698

Table 4 (continued)

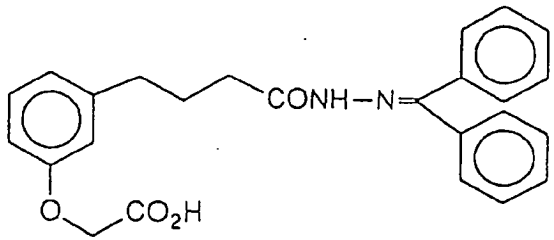
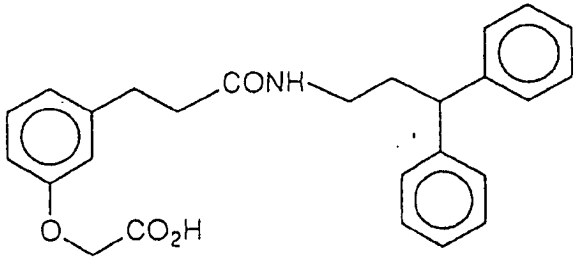
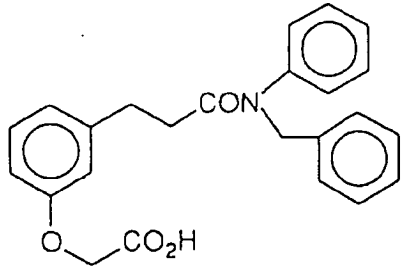
EX. No.	Structure of the example compound	TLC	IR (cm^{-1})
8 (s)		Rf 0.50 (methylene chloride : methanol = 10:3)	[KBr method] ν 3482. 3159. 3053. 2965. 2905. 2759. 2524. 1746. 1637. 1584. 1489. 1457. 1432. 1397. 1359. 1322. 1309. 1272. 1229. 1156. 1087. 1028. 956. 927. 873. 774. 741. 695. 637. 600. 523. 463. 431
8 (t)		Rf 0.32 (methylene chloride : methanol = 10:3)	[KBr method] ν 3326. 3023. 2920. 2880. 1719. 1585. 1494. 1484. 1451. 1435. 1378. 1312. 1293. 1249. 1208. 1168. 1091. 894. 865. 785. 770. 750. 696. 606. 585. 495. 468
8 (u)		Rf 0.49 (methylene chloride : methanol = 10:3)	ν 3031. 2931. 1746. 1613. 1587. 1495. 1454. 1416. 1266. 1211. 1159. 1082. 1018. 983. 778. 756. 700

Table 4 (continued)

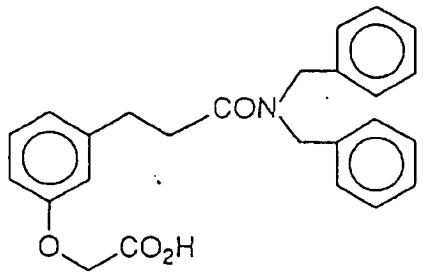
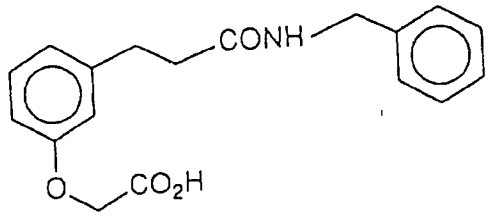
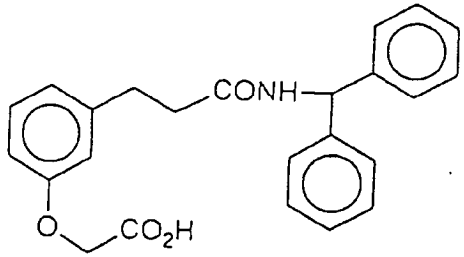
EX. No.	Structure of the example compound	TLC	IR (cm^{-1})
8 (v)		Rf 0.53 (methylene chloride : methanol = 10:3)	ν 3030. 2927. 1746. 1603. 1494. 1452. 1361. 1217. 1161. 1082. 1029. 1002. 956. 883. 752. 699
8 (w)		Rf 0.21 (methylene chloride : methanol = 10:3)	[KBr method] ν 3347. 3293. 3033. 2935. 1742. 1712. 1640. 1610. 1587. 1547. 1492. 1454. 1432. 1350. 1301. 1281. 1213. 1159. 1104. 1080. 1020. 922. 887. 781. 749. 695. 498. 456
8 (x)		Rf 0.43 (methylene chloride : methanol = 10:3)	[KBr method] ν 3326. 3061. 1752. 1651. 1614. 1585. 1535. 1496. 1455. 1427. 1381. 1299. 1246. 1220. 1166. 1106. 980. 922. 874. 789. 769. 745. 697. 640. 532

Table 4 (continued)

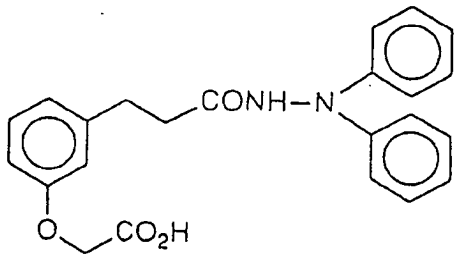
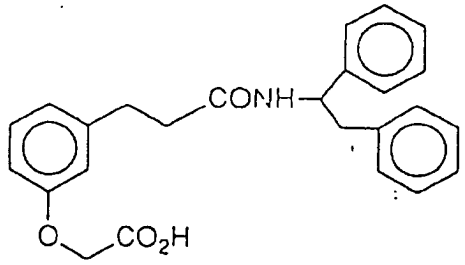
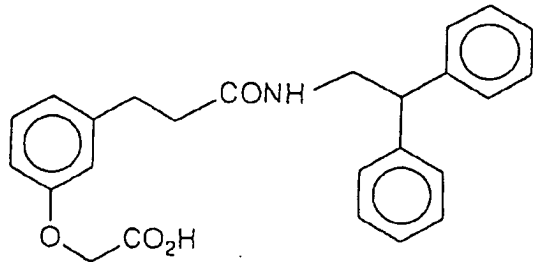
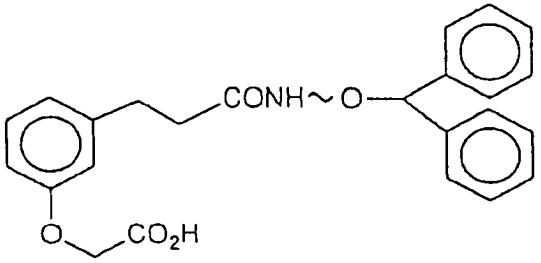
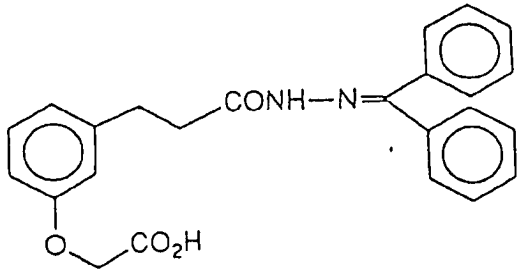
EX. No.	Structure of the example compound	TLC	IR (cm^{-1})
8 (y)		Rf 0.40 (methylene chloride : methanol = 10:3)	[KBr method] ν 3279. 1737. 1704. 1673. 1589. 1523. 1496. 1453. 1414. 1301. 1280. 1234. 1160. 1086. 921. 771. 747. 693. 630. 507
8 (z)		Rf 0.38 (methylene chloride : methanol = 10:3)	[KBr method] ν 3328. 3063. 3030. 2916. 2582. 1752. 1641. 1595. 1537. 1495. 1455. 1432. 1319. 1300. 1251. 1175. 1094. 1030. 913. 847. 790. 759. 699. 644. 539. 508
8 (na)		Rf 0.50 (methylene chloride : methanol = 10:3)	[KBr method] ν 3339. 3060. 2931. 1737. 1603. 1561. 1484. 1452. 1224. 1159. 1087. 1032. 1008. 881. 783. 755. 742. 701. 586. 540

Table 4 (continued)

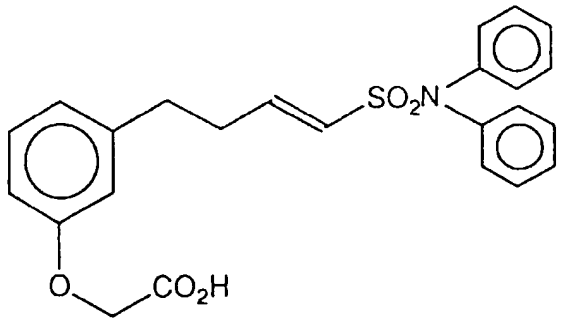
EX. No.	Structure of the example compound	TLC	IR (cm^{-1})
8 (bb)		Rf 0.33 (methylene chloride : methanol = 10:3)	[KBr method] ν 3209. 3032. 1736. 1656. 1494. 1452. 1229. 1161. 1084. 1002. 876. 762. 746. 699
8 (cc)		Rf 0.48 (methylene chloride : methanol = 10:3)	[KBr method] ν 3181. 3070. 3025. 2924. 2524. 1736. 1631. 1584. 1490. 1460. 1440. 1397. 1335. 1313. 1284. 1265. 1232. 1159. 1113. 1094. 1030. 958. 929. 912. 881. 783. 772. 736. 691. 637. 612. 597. 545. 470. 443.

The example compounds shown in the table 4 are named as follows:

8(a) 3-(N-Benzyl-N-phenylaminocarbonylmethyl)phenoxyacetic acid,
8(b) 3-(N,N-Dibenzylaminocarbonylmethyl)phenoxyacetic acid,
8(c) 3-(N-Benzylaminocarbonylmethyl)phenoxyacetic acid,
8(d) 3-(Diphenylmethylaminocarbonylmethyl)phenoxyacetic acid,
8(e) 3-[(N,N-Diphenylamino)aminocarbonylmethyl]phenoxyacetic acid,
8(f) 3-(1,2-Diphenylethylaminocarbonylmethyl)phenoxyacetic acid,
8(g) 3-(2,2-Diphenylethylaminocarbonylmethyl)phenoxyacetic acid,
8(h) 3-(Diphenylmethyloxyaminocarbonylmethyl)phenoxyacetic acid,
8(i) 3-[(1,1 -Diphenylmethylideneamino)aminocarbonylmethyl]phenoxyacetic acid,
8(j) 3-[3-(3,3-Diphenylpropylaminocarbonyl)propyl]phenoxyacetic acid,
8(k) 3-[3-(N-Benzyl-N-phenylaminocarbonyl)propyl]phenoxyacetic acid,
8(l) 3-[3-(N,N-Dibenzylaminocarbonyl)propyl]phenoxyacetic acid,
8(m) 3-(3-Benzylaminocarbonylpropyl)phenoxyacetic acid,
8(n) 3-(3-Diphenylmethylaminocarbonylpropyl)phenoxyacetic acid,
8(o) 3-[3-[(N,N-Diphenylamino)aminocarbonyl]propyl]phenoxyacetic acid,
8(p) 3-[3-(1,2-Diphenylethylaminocarbonyl)propyl]phenoxyacetic acid,
8(q) 3-[3-(2,2-Diphenylethylaminocarbonyl)propyl]phenoxyacetic acid,
8(r) 3-(3-Diphenylmethyloxyaminocarbonylpropyl)phenoxyacetic acid,
8(s) 3-[3-[(1,1-Diphenylmethylideneamino)aminocarbonyl]propyl]phenoxy acetic acid,
8(t) 3-[2-(3,3-Diphenylpropylaminocarbonyl)ethyl]phenoxyacetic acid,
8(u) 3-[2-(N-Benzyl-N-phenylaminocarbonyl)ethyl]phenoxyacetic acid,
8(v) 3-[2-(N,N-Dibenzylaminocarbonyl)ethyl]phenoxyacetic acid,
8(w) 3-(2-Benzylaminocarbonylethyl)phenoxyacetic acid,
8(x) 3-(2-Diphenylmethylaminocarbonylethyl)phenoxyacetic acid,
8(y) 3-[2-[(N,N-Diphenylamino)aminocarbonyl]ethyl]phenoxyacetic acid,
8(z) 3-[2-(1,2-Diphenylethylaminocarbonyl)ethyl]phenoxyacetic acid,
8(aa) 3-[2-(2,2-Diphenylethylaminocarbonyl)ethyl]phenoxyacetic acid,
8(bb) 3-(2-Diphenylmethyloxyaminocarbonylethyl)phenoxyacetic acid,
8(cc) 3-[2-[(1,1-Diphenylmethylideneamino)aminocarbonyl]ethyl]phenoxy acetic acid,

Example 9

3-(4-Diphenylaminosulfonyl-3-butenyl)phenoxyacetic acid

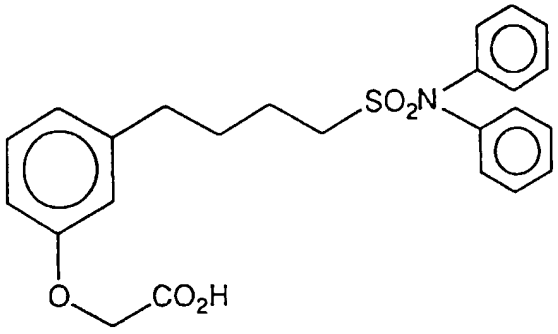


To a solution of the compound (0.08 g) prepared by the same procedure as in reference example 1, using the compound prepared in reference example 8, in acetone (2.0 ml) was added 8N Jone's reagent (0.1 ml) at 0 °C. After stirred for 10 min at 0 °C, the mixture was added isopropyl alcohol (0.5 ml). The mixture was stirred for 10 min, added water, and extracted with ether. The extract was washed with water and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (methylene chloride → methylene chloride : methanol = 40 : 1) to give the title compound (0.035 g) having the following physical data.
TLC: Rf 0.18 (methylene chloride : methanol = 5 : 1);

IR [KBr tablet method] (cm^{-1}): ν 3435, 3051, 2928, 1749, 1714, 1611, 1586, 1489, 1452, 1424, 1353, 1262, 1224, 1193, 1164, 1147, 1091, 1027, 1011, 975, 912, 865, 824, 781, 757, 694, 631, 596, 547.

Example 10

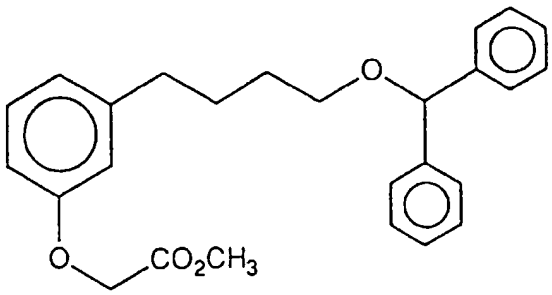
3-(4-Diphenylaminosulfonylbutyl)phenoxyacetic acid



To a solution of the compound prepared in example 9 (410 mg) in ethyl acetate (5.0 ml) was added excess amount of diazomethane in ether at 0 °C. After 10 min, the mixture was evaporated. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 2 : 1) to give methyl ester compound (56 mg). To a solution of the methyl ester compound (56 mg) in methanol (5 ml) was added 10% palladium on activated carbon (50 mg) at room temperature. The mixture was vigorously stirred for 6h under an atmosphere of hydrogen. The catalyst was removed by filtration through Celite. Evaporation of the solvent gave (54 mg) of the residue. By the same procedure as in example 2, using the residue, the title compound (36 mg) having physical data was given.
TLC: Rf 0.21 (methylene chloride : methanol = 5 : 1);
IR [KBr tablet method] (cm^{-1}): ν 2925, 2862, 2590, 1750, 1710, 1612, 1586, 1488, 1463, 1451, 1424, 1350, 1302, 1287, 1258, 1243, 1218, 1197, 1164, 1146, 1103, 1078, 1027, 1012, 978, 913, 865, 780, 759, 708, 695, 626, 594, 534.

Example 11

Methyl 3-(4-diphenylmethyloxybutyl)phenoxyacetate

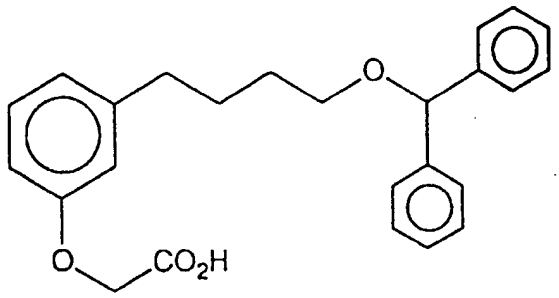


To a solution of methyl 3-(4-hydroxybutyl)phenoxyacetate (372 mg) and diphenylmethyltrichloroacetoimidate (771 mg) in chloroform (4 ml) and cyclohexane (8 ml) was added a catalytic amount of boron trifluoride etherate at 0 °C. After stirred for 30 min at 0 °C, the mixture was quenched by addition of a saturated aqueous solution of sodium bicarbonate, and extracted with ether. The extract was washed with water and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 4 : 1) to give the title compound (343 mg) having the following physical data.
NMR: δ 7.50-7.00 (11 H, m), 6,90-6.50 (3H, m), 5.27 (1H, s), 4.58 (2H, s), 3.77 (3H, s), 3.43 (2H, t, J=7Hz), 2.58 (2H, t, J=7Hz), 1.68 (4H, m);

IR (cm^{-1}): ν 3029, 2938, 2860, 1762, 1586, 1494, 1453, 1211, 1159, 1095, 1029, 743, 699.

Example 12

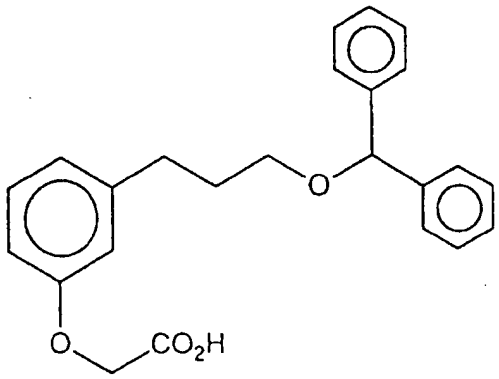
3-(4-Diphenylmethyloxybutyl)phenoxyacetic acid



By the same procedure as in example 2, using the compound prepared in example 11 (340 mg), the title compound (277 mg) having the following physical data was given.
TLC: Rf 0.18 (chloroform : methanol = 9 : 1);
IR (cm^{-1}): ν 3030, 2938, 2862, 1733, 1586, 1494, 1454, 1242, 1160, 1094, 761, 744, 699.

Example 12(a)

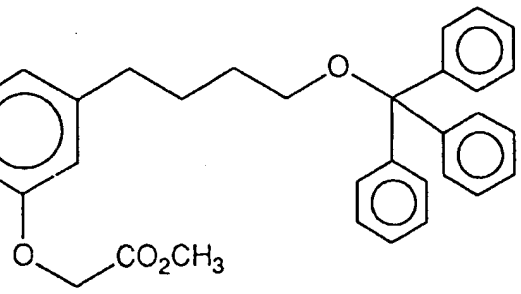
3-(3-Diphenylmethyloxypropyl)phenoxyacetic acid



By the same procedure as in example 11 → example 2, using methyl 3-(3-hydroxypropyl)phenoxyacetate instead of methyl 3-(4-hydroxybutyl) phenoxycacetate, the title compound having the following physical data was given.
mp.: 110-112 °C;
TLC: Rf 0.15 (ethyl acetate);
IR [KBr tablet method] (cm^{-1}): ν 2861, 1748, 1710, 1594, 1494, 1431, 1398, 1307, 1237, 1174, 1105, 1083, 1059, 1030, 904, 859, 783, 741, 697, 651, 612.

Example 13

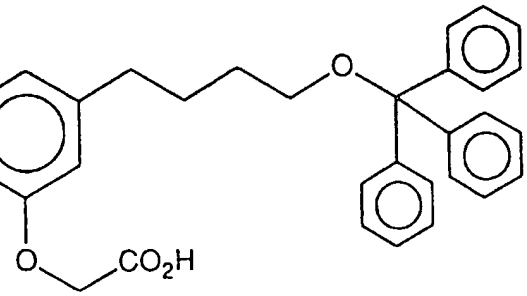
Methyl 3-(4-triphenylmethoxybutyl)phenoxyacetate



To a solution of methyl 3-(4-hydroxybutyl) phenoxyacetate (174 mg) in dimethylformamide (8.0 ml) was added successively trityl chloride (223 mg) and N,N-dimethylaminopyridine (88 mg). After stirred overnight at room temperature, the mixture was quenched by addition of water and extracted with ether. The extract was washed with water and a saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by flash silica gel chromatography (n-hexane: ethyl acetate = 4 : 1) to give the title compound (228 mg) having the following physical data.
NMR: δ7.50-7.00 (16H, m), 6.90-6.50 (3H, m), 4.58 (2H, s), 3.78 (3H, s), 3.04 (2H, t, J=7Hz), 2.53 (2H, m), 1.66 (4H, m);
IR (cm^{-1}): ν 3057, 2938, 2865, 1764, 1741, 1586, 1490, 1449, 1289, 1211, 1158, 1075, 1033, 764, 707.

Example 14

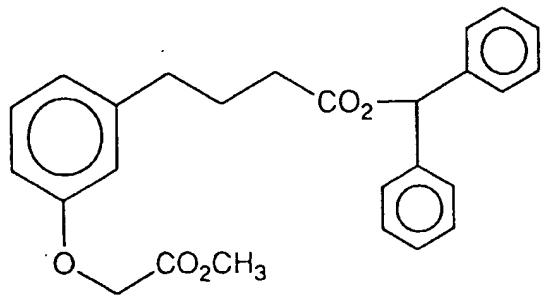
3-(4-Triphenylmethoxybutyl)phenoxyacetic acid



By the same procedure as in example 2, using the compound prepared in example 13 (220 mg), the title compound (159 mg) having the following physical data was given.
TLC: Rf 0.13 (chloroform : methanol = 9 : 1);
IR (cm^{-1}): ν 3058, 2937, 2866, 1738, 1586, 1490, 1449, 1240, 1159, 1075, 900, 764, 698.

Example 15

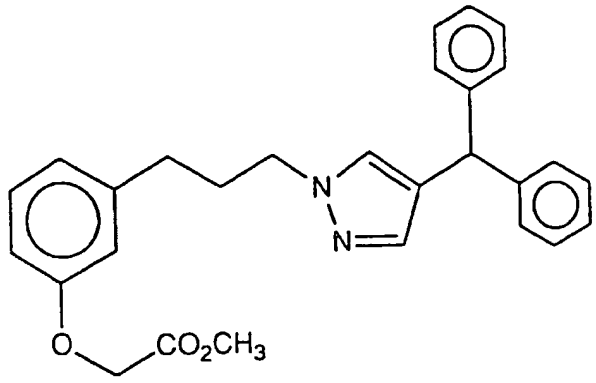
Methyl 3-(3-diphenylmethyloxycarbonylpropyl)phenoxyacetate



A mixture of 3-(3-methoxycarbonylmethoxyphenyl)propionic acid (195 mg), 2-chloro-N-methylpyridinium iodide (297 mg), diphenylmethanol (185 mg), triethylamine (0.32 ml), and catalytic amount of N,N-dimethyaminopyridine in methylene chloride (6 ml) was stirred overnight at room temperature. The mixture was poured into 1N hydrochloric acid extracted with ethyl acetate. The extract was washed with water and saturated aqueous solution of sodium chloride, successively, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (n-hexane : ethyl acetate = 4 : 1) to give the title compound (128 mg) having the following physical data.
TLC: Rf 0.54 (n-hexane : ethyl acetate = 7 : 3);
NMR: δ 7.40-7.10 (11H, m), 6.89 (1H, s), 6.85-6.60 (3H, m), 4.60 (2H, s), 3.79 (3H, s), 2.60 (2H, t, J=6 Hz), 2.43 (2H, t, J=7 Hz), 1.97 (2H, m).

Reference Example 25

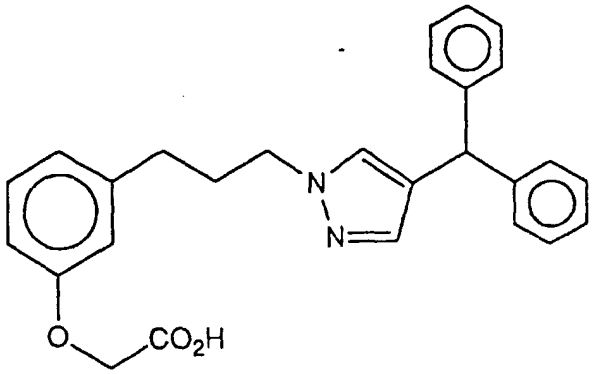
Methyl 3-[3-(4-diphenylmethylpyrazol-1-yl)propyl]phenoxyacetate



To a suspension of sodium hydride (217 mg, 60% dispersion) in dimethylformamide (10 ml) was added dropwise a solution of 4-diphenylmethylpyrazole (1.27 g) in dimethylformamide (50 ml) at room temperature. After stirred for 30 min at room temperature, to the mixture was added dropwise a solution of the compound prepared in reference example 9(1.56 g) in dimethylformamide. After stirred for 1h, the mixture was quenched by addition of 1N hydrochloric acid and extracted with a mixture of ethyl acetate-n-hexane (1 : 2). The extract was washed with saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (ethyl acetate : n-hexane = 3 : 7) to give the title compound (2.01 g) having the following physical data.
TLC: Rf 0.59 (n-hexane : ethyl acetate = 1 : 1);
NMR: δ 7.40-7.10 (12H, m), 6.93 (1H, s), 6.80-6.60 (3H, m), 5.35 (1H, s), 4.58 (2H, s), 4.03 (2H, t, J=7Hz), 3.79 (3.H, s), 2.56 (2H, t, J=7Hz), 2.16(2H, m).

Reference Example 26

3-[3-(4-diphenylmethylpyrazol-1-yl)propyl]phenoxyacetic acid



By the same procedure as in example 2, using the compound prepared in reference example 25 (1.5g), the title compound (1.1 g) having the following physical data was given.
TLC: Rf 0.21 (chloroform : methanol = 4 : 1);
IR [KBr tablet method] (cm^{-1}): ν 3027, 2930, 1736, 1586, 1493, 1451, 1219, 1159, 1079, 1014, 874, 753, 701, 507.

Example 17(a)-17 (g)

By the same procedure as in reference example 9 → reference example 25 → reference example 26, using corresponding compounds, compounds having the following physical data shown in the table 5 were given.

Table 5

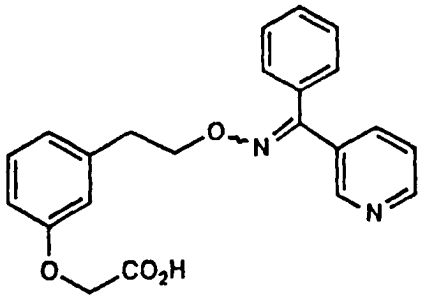
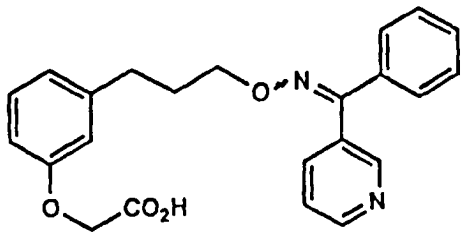
EX. No.	Structure of the example compound	TLC (Rf)	N M R (δ)
17(a)		0.40 (methanol: methylene chloride = 1 : 4)	8.63 and 8.47 (1H,s), 8.56 and 8.53 (1H, d), 7.78-7.73 and 7.62-7.37 (1H,m), 7.45-7.22 (6H, m), 7.16-7.09 (1H, m), 6.79-6.65 (3H, m), 4.43 (2H, s), 4.38-4.33 (2H, m), 2.96-2.88 (2H, m)
17(b)		0.49 (methanol: methylene chloride = 1 : 4)	8.71 and 8.62 (1H, s), 8.61 and 8.55 (1H, d), 7.80-7.76 and 7.70-7.67 (1H, m), 7.50-7.25 (6H, m), 7.13-7.06 (1H, m), 6.75-6.65 (3H, m), 4.45 (2H, s), 4.20-4.10 (2H, m), 2.60-2.50 (2H, m), 2.01-1.92 (2H, m)

Table 5 (continued)

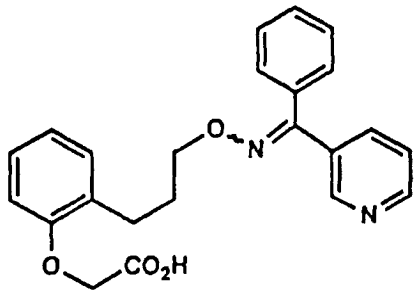
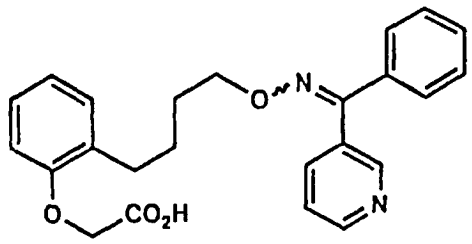
EX. No.	Structure of the example compound	TLC (Rf)	N M R (δ)
17(c)		0.46 (methanol: methylene chloride =1 : 4)	8.81 and 8.67 (1H,s), 8.57 and 8.52 (1H, d), 7.73-7.65 (1H,m), 7.50-7.20 (6H, m), 7.10-7.05 (2H, m), 6.85 (1H, t), 6.73 (1H, d), 4.51 and 4.48 (2H, s), 4.25-4.18 (2H, m), 2.75-2.65 (2H, m), 2.10-1.98 (2H, m)
17(d)		0.46 (methanol: methylene chloride =1 : 4)	8.71 and 8.62 (1H, s), 8.55 and 8.52 (1H, d), 7.78-7.74 and 7.70-7.66 (1H, m), 7.47-7.15 (6H, m), 7.13-7.08 (2H, m), 6.88 (1H, t), 6.74 (1H, d), 4.54 (2H, s), 4.25-4.18 (2H, m), 2.73-2.65 (2H, m), 1.80-1.60 (4H, m).

Table 5 (continued)

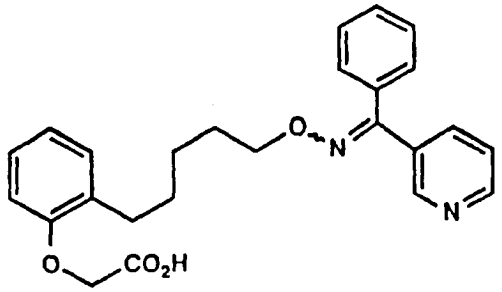
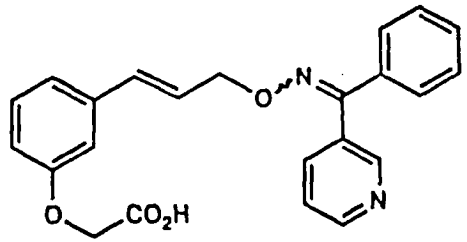
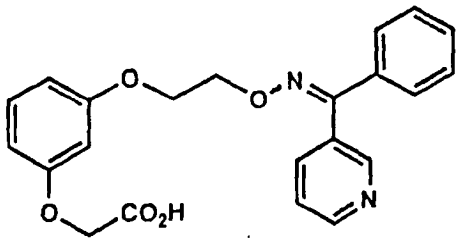
EX. No.	Structure of the example compound	TLC (Rf)	N M R (δ)
17(e)		0.43 (methanol: methylene chloride = 1 : 4)	8.72 and 8.64 (1H,s), 8.59-8.50 (1H, m), 7.78-7.73 and 7.68-7.65 (1H,m), 7.46-7.15 (6H, m), 7.14-7.07 (2H, m), 6.90-6.85 (1H, m), 6.78-6.73 (1H, m), 4.52 (2H, s), 4.18 (2H, t), 2.67 (2H, t), 1.80-1.69 (2H, m), 1.69-1.56 (2H, m), 1.44-1.34 (2H, m)
17(f)		0.22 (methanol: methylene chloride = 1 : 5)	8.80 (0.4H, d), 8.70 (0.6H, d), 8.67 (0.6H, dd), 8.62 (0.4H, dd), 7.87-7.72 (1H, m), 7.60-6.90 (9H, m), 6.90-6.78 (1H, m), 6.63 (0.4H, d), 6.55 (0.6H, d), 6.37 (0.6H, dt), 6.30 (0.4H, dt), 4.92-4.77 (2H, m), 4.67 (0.8H, s), 4.65 (1.2H, s).

Table 5 (continued)

EX. No.	Structure of the example compound	TLC (Rf)	N M R (δ)
17(g)		0.43 (methanol: methylene chloride = 1 : 4)	8.67 and 8.57 (1H,s), 8.56 and 8.53 (1H, d), 7.77-7.73 and 7.70-7.65 (1H,m), 7.45-7.25 (6H, m), 7.13-7.06 (1H, m), 6.55-6.45 (3H, m), 4.55-4.40 (4H, m), 4.25-4.15 (2H, m)

The example compounds shown in the table 5 are named as follows:

17(a) 3-[2-[1-Phenyl-1-(3-pyridyl)methylideneaminooxy]ethyl]phenoxyacetic acid,
17(b) 3-[3-[1-Phenyl-1-(3-pyridyl)methylideneaminooxy]propyl]phenoxyacetic acid,
17(c) 2-[3-[1-Phenyl-1-(3-pyridyl)methylideneaminooxy]propyl]phenoxyacetic acid,
17(d) 2-[4-[1-Phenyl-1-(3-pyridyl)methylideneaminooxy]butyl]phenoxyacetic acid,
17(e) 2-[5-[1-Phenyl-1-(3-pyridyl)methylideneaminooxy]pentyl]phenoxy acetic acid,
17(f) 3-[3-[1-Phenyl-1-(3-pyridyl)methylideneaminooxy]-1-propenyl]phenoxy acetic acid,
17(g) 3-[2-[1-Phenyl-1(3-pyridyl)methylideneaminooxy]ethyloxy]phenoxy acetic acid

Formulation example 1

The following components were admixed in conventional method and punched out to obtain 100 tablets each containing 5 mg of active ingredient.

- 3-(4-Diphenylmethyloxyiminobutyl)phenoxy acetic acid 500 mg
- Carboxymethylcellulose calcium 200 mg
- Magnesium stearate 100 mg
- Microcrystalline cellulose 9.2 g

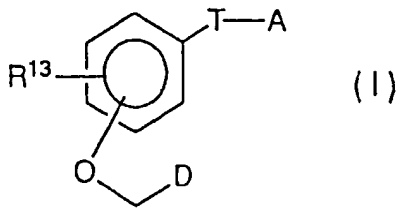
Formulation example 2

The following components were admixed in conventional manner. The solution was sterilized in conventional manner, placed 5 ml portion into 10 ml ampoules and freeze-dried to obtain 100 ampoules each containing 2 mg of the active ingredient.

- 3-(4-Diphenylmethyloxyiminobutyl)phenoxy acetic acid 200 mg
- Citric acid, anhydrous 20 mg
- Distilled water 500 ml

Claims

1. A Phenoxyacetic acid derivative of the formula (I):



(I)

wherein

A is
i) $-CR^1=N\sim OR^2$,
ii) $-CHR^1-NH-OR^2$,
iii) -COE,
iv) $-SO_2E$,
v) $-CH_2-NR^3-Y$,
vi) $-Z-NR^3-CONR^4R^5$,
vii) $-CH_2-OR^6$,
viii) $-CO_2R^6$,
ix) $-CH_2-O\sim N=CR^7R^8$ or
x) $-CH_2-O-NHCHR^7R^8$,

T is	i) single bond, ii) C1-6 alkylene, iii) C2-6 alkenylene or iv) -O-$(CH_2)_s$-;
D is	i) $-CO_2R^{10}$ or ii) $-CONR^{11}R^{12}$;
E is	i) $-NR^4R^5$, ii) $-NR^3OR^6$, iii) $-NR^3-NR^4R^5$ or iv) $-NR^3-N=CR^4R^5$;
Y is	i) $-COR^6$, ii) -CO-L-NR^4R^5, iii) -CS-NHR^4 or iv) $-SO_2R^6$;
Z is	i) -CH=N- or ii) $-CH_2-NR^3$-;
L is	single bond or C1-4 alkylene;
R^1 is	hydrogen, C1-6 alkyl or phenyl;
R^2 is	i) C1-8 alkyl substituted by one or two of phenyl, 4-7 membered monocyclic hetero ring containing one nitrogen or C4-7 cycloalkyl, ii) C10-15 hydrocarbon condensed tricyclic ring or iii) C1-15 alkyl;
R^3 is	hydrogen, C1-6 alkyl or phenyl;
R^4 and R^5 each, independently, is	i) hydrogen, ii) phenyl, iii) 4-7 membered monocyclic hetero ring containing one nitrogen or iv) C1-4 alkyl substituted by one or two of phenyl or 4-7 membered monocyclic hetero ring containing one nitrogen;
R^6 is	i) phenyl, ii) 4-7 membered monocyclic hetero ring containing one nitrogen or iii) C1-4 alkyl substituted by one to three of phenyl or 4-7 membered monocyclic hetero ring containing one nitrogen;
R^7 is	i) hydrogen, ii) C1-8 alkyl, iii) phenyl or C4-7 cycloalkyl, iv) 4-7 membered monocyclic hetero ring containing one nitrogen or v) C1-4 alkyl substituted by one or two of phenyl, C4-7 cycloalkyl or 4-7 membered monocyclic hetero ring containing one nitrogen;
R^8 is	i) C1-8 alkyl, ii) phenyl or C4-7 cycloalkyl iii) 4-7 membered monocyclic hetero ring containing one nitrogen or iv) C1-4 alkyl substituted by one or two of phenyl, C4-7 cycloalkyl or 4-7 membered monocyclic hetero ring containing one nitrogen;
R^{10} is	hydrogen or C1-12 alkyl;

R^{11} and R^{12} each, independently, is	hydrogen or C1-4 alkyl or
R^{11} and R^{12},	taken together with nitrogen bond to R^{11} and R^{12} is the residue of an amino acid;
R^{13} is	hydrogen, C1-4 alkyl, C1-4 alkoxy or nitro;
s is	2-4;

and the rings of R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 may be also substituted by one to three of C1-C4 alkyl, C1-C4 alkoxy, halogen, nitro or trihalomethyl;
with the proviso that,

1) when A is $-SO_2E$ wherein E is the same meaning hereinbefore defined, T is not single bond and C1 alkylene (methylene),
(2) the compounds wherein A is -CONH-phenyl (phenyl may be substituted by 1-3 of C1-4 alkyl, C1-4 alkoxy, halogen or NO_2) are excluded,

and non-toxic salts thereof and non-toxic acid addition salts thereof.

(2) A compound according to claim 1, wherein D is carboxy.

(3) A compound according to claim 1, wherein D is C1-12 alkoxycarbonyl.

(4) A compound according to claim 1, wherein D is $CONR^{11}R^{12}$ in which R^{11} and R^{12} are the same meaning as defined in claim 1.

(5) A compound according to claim 1, wherein

A is i) $-CR^1=N\sim OR^2$,
ii) $-CHR^1-NH-OR^2$,
ix) $-CH_2-O\sim N=CR^7R^8$ or
x) $-CH_2-O-NHCHR^7R^8$

in which all the symbols are the same meaning as defined in claim 1.

(6) A compound according to claim 1, wherein

A is iii) -COE,
iv) $-SO_2E$
v) $-CH_2NR^3-Y$ or
vi) $-Z-NR^3-CONR^4R^5$

in which all the symbols are the same meaning as defined in claim 1.

(7) A compound according to claim 1, wherein

A is vii) $-CH_2OR^6$

in which R^6 is the same meaning as defined in claim 1.

(8) A compound according to claim 1, wherein

A is viii) $-CO_2R^6$

in which R^6 is the same meaning as defined in claim 1.

(9) A compound according to claim 5, which is

3-(4-Diphenylmethyloxyiminobutyl)phenoxyacetic acid,
4-(3-Diphenylmethyloxyiminopropyl)phenoxyacetic acid,

4-(4-Diphenylmethyloxyiminobutyl)phenoxyacetic acid
3-(3-Diphenylmethyloxyiminopropyl)phenoxyacetic acid,
3-(4-Diphenylmethyloxyiminoheptyl)phenoxyacetic acid,
3-(4-Diphenylmethyloxyaminoheptyl)phenoxyacetic acid,
3-[2-[2-Phenyl-2-(3-pyridyl)ethyl]oxyiminoethyl]phenoxyacetic acid,
3-[2-[2-Cyclohexyl-2-phenylethyl)oxyiminoethyl]phenoxyacetic acid,
3-[2-[2-(Fluorene-9-yl)ethyl]oxyiminoethyl]phenoxyacetic acid,
3-[2-(2-Phenyldecyl)oxyiminoethyl]phenoxyacetic acid,
3-[2-Di(3-pyridyl)methyloxyiminoethyl]phenoxyacetic acid,
3-[4-Methyl-4-(1-phenyl-1-(3-pyridyl)methyloxyimino)butyl]phenoxyacetic acid,
3-[2-[1-Phenyl-1-(3-pyridyl)methylideneaminooxy]ethyl]phenoxyacetic acid,
3-[3-[1-Phenyl-1-(3-pyridyl)methylideneaminooxy]propyl]phenoxyacetic acid,
2-[3-[1-Phenyl-1-(3-pyridyl)methylideneaminooxy]propyl]phenoxyacetic acid,
2-[4-[1-Phenyl-1-(3-pyridyl)methylideneaminooxy]butyl]phenoxyacetic acid,
2-[5-[1-Phenyl-1-(3-pyridyl)methylideneaminooxy]pentyl]phenoxyacetic acid,
3-[3-[1-Phenyl-1-(3-pyridyl)methylideneaminooxy]-1-propenyl]phenoxyacetic acid,
3-[2-[1-Phenyl-1-(3-pyridyl)methylideneaminooxy]ethyloxy]phenoxyacetic acid,
3-[3-[Di(3-pyridyl)methylideneaminooxy]propyl]phenoxyacetic acid,
3-[3-[1-Cyclohexyl-1-phenylmethylideneaminooxy]propyl]phenoxyacetic acid,
2-Methyl-3-[3-[1-phenyl-1-(3-pyridyl)methylideneaminooxy]propyl]phenoxy acetic acid,
3-[3-[1-Phenyl-1-(3-pyridyl)methylaminooxy]propyl]phenoxyacetic acid

or its methyl ester, or its octyl ester, or its acetamide, its amide with glycine.

(10) A compound according to claim 6, which is

3-(3,3-Diphenylpropylaminocarbonylmethyl)phenoxyacetic acid,
3-(N-Benzyl-N-phenylaminocarbonylmethyl)phenoxyacetic acid,
3-(N,N-Dibenzylaminocarbonylmethyl)phenoxyacetic acid,
3-(N-Benzylaminocarbonylmethyl)phenoxyacetic acid,
3-(Diphenylmethylaminocarbonylmethyl)phenoxyacetic acid,
3-[(N,N-Diphenylamino)aminocarbonylmethyl]phenoxyacetic acid,
3-(1,2-Diphenylethylaminocarbonylmethyl)phenoxyacetic acid,
3-(2,2-Diphenylethylaminocarbonylmethyl)phenoxyacetic acid,
3-(Diphenylmethyloxyaminocarbonylmethyl)phenoxyacetic acid,
3-[(1,1-Diphenylmethylideneamino)aminocarbonylmethyl]phenoxyacetic acid,
3-[3-(3,3-Diphenylpropylaminocarbonyl)propyl]phenoxyacetic acid,
3-[3-(N-Benzyl-N-phenylaminocarbonyl)propyl]phenoxyacetic acid,
3-[3-(N,N-Dibenzylaminocarbonyl)propyl]phenoxyacetic acid,
3-(3-Benzylaminocarbonylpropyl)phenoxyacetic acid,
3-(3-(3-Diphenylmethylaminocarbonylpropyl)phenoxyacetic)phenoxyacetic acid,
3-[3-[(N,N-Diphenylamino)aminocarbonyl]propyl]phenoxyacetic acid,
3-[3-(1,2-Diphenylethylaminocarbonyl)propyl]phenoxyacetic acid,
3-[3-(2,2-Diphenylethylaminocarbonyl)propyl]phenoxyacetic acid,
3-(3-(3-Diphenylmethyloxyaminocarbonylpropyl)phenoxyacetic acid,
3[3-[1,1-Diphenylmethylideneamino)aminocarbonyl]propyl]phenoxyacetic acid,
3-[2-(3,3-Diphenylpropylaminocarbonyl)ethyl]phenoxyacetic acid,
3-[2-(N-Benzyl-N-phenylaminocarbonyl)ethyl]phenoxyacetic acid,
3-[2-(N,N-Dibenzylaminocarbonyl)ethyl]phenoxyacetic acid,
3-(2-Benzylaminocarbonylethyl)phenoxyacetic acid,
3-(2-Diphenylmethylaminocarbonylethyl)phenoxyacetic acid,
3-[2-[(N,N-Diphenylamino)aminocarbonyl]ethyl]phenoxyacetic acid,
3-[2-(1,2-Diphenylethylaminocarbonyl)ethyl]phenoxyacetic acid,
3-[2-(2,2-Diphenylethylaminocarbonyl)ethyl]phenoxyacetic acid,
3-(2-Diphenylmethyloxyaminocarbonylethyl)phenoxyacetic acid,
3-[2-[(1,1-Diphenylmethylideneamino)aminocarbonyl]ethyl]phenoxyacetic acid,
3-(4-Diphenylaminosulfonyl-3-butenyl)phenoxyacetic acid,
3-(4-Diphenylaminosulfonylbutyl)phenoxyacetic acid,

4-(2-Benzoylaminoethyl)phenoxyacetic acid,
4-[2-(N,N-Diphenylaminocarbonylamino)ethyl]phenoxyacetic acid,
4-[2-(N,N-Diphenylaminomethylcarbonylamino)ethyl]phenoxyacetic acid,
4-(2-Phenylaminothiocarbonylaminoethyl)phenoxyacetic acid,
4-(2-Phenylsulfonylaminoethyi)phenoxyacetic acid,
4-[2-(N,N-Diphenylaminocarbonylaminoimino)ethyl]phenoxyacetic acid,
3-(3-(3-Diphenylmethyloxyaminosulfonylpropyl)phenoxyacetic acid,
3-[3-[(N,N-Diphenylamino)aminosulfonyl]propyl]phenoxyacetic acid,
3-[3-[(1,1-Diphenylmethylideneamino)aminosulfonyl]propyl]phenoxyacetic acid,
4-[2-[(N, N-Diphenylaminocarbonylamino)amino]ethyl]phenoxyacetic acid,
or its methyl ester, or its octyl ester, or its acetamide, its amide with glycine.

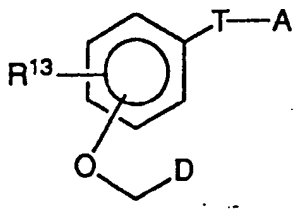
(11) A compound according to claim 7, which is

3-(4-Diphenylmethyloxybutyl)phenoxyacetic acid,
3-(3-Diphenylmethyloxypropyl)phenoxyacetic acid,
3-(4-Triphenylmethoxybutyl)phenoxyacetie acid,

or its methyl ester, or its octyl ester, or its acetamide, its amide with glycine.

(12) A compound according to claim 8, which is
3-(3-Diphenylmethyloxycarbonylpropyl)phenoxyacetic acid,
or its methyl ester, or its octyl ester, or its acetamide, its amide with glycine.

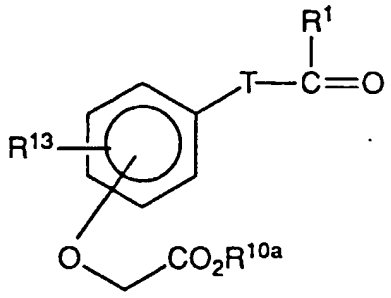
(13) A process for the preparation of phenoxyacetic acid derivatives of the fomula (I):



(I)

wherein aii symbols are the meaning as hereinbefore defined in claim 1 or salts thereof or acid addtion salts thereof, which is characterized by:

(i) the reaction of a compound of the formula (III):



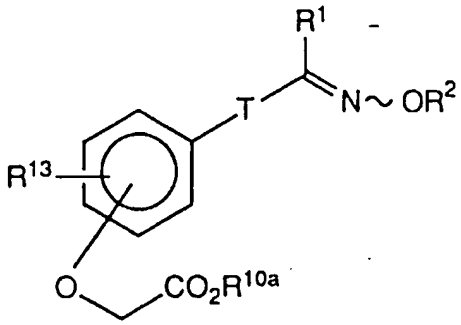
(III)

wherein R^{10a} menas methyl or ethyl and the other symbols are the same meaning as hereinbefore defined, with a compound of the formula (a):

$$R^2ONH_2 \qquad (a)$$

wherein R^2 is the same meaning as hereinbefore defined,

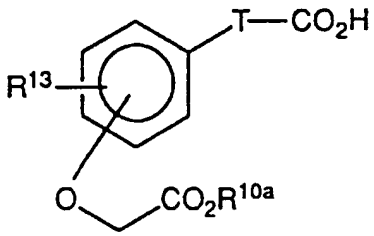
(ii) subjecting a compound obtained by reaction (i) of the formula (Ia-1):



(Ia-1)

wherein all the symbols are the same meaning as hereinbefore defined, to reduction,

(iii) the amidation of a compound of the formula (IV):



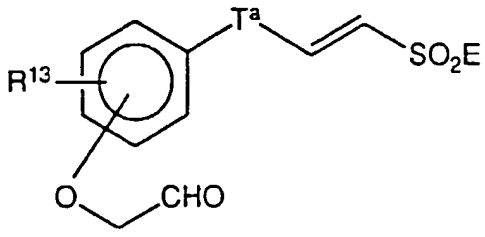
(IV)

wherein all the symbols are the same meaning as hereinbefore defined, with a compound of the formula (b):

H E (b)

wherein E is the same meaning as hereinbefore defined,

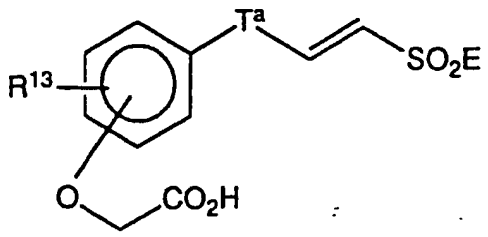
(iv) subjecting a compound of the formula (VI):



(VI)

wherein T^a is single bond, C1-4 alkylene, C2-4 alkenylene, or $-O-(CH_2)_t-$ wherein t is 0-2, and the other symbols are the same meaning as hereinbefore defined, to Jone's oxidation,

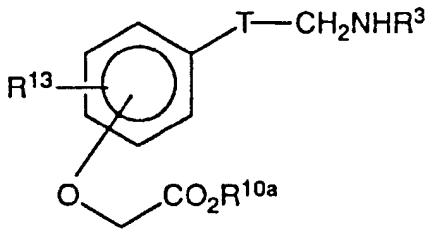
(v) subjecting a compound obtained by reaction (iv) of the formula (Ib-1):



(Ib-1)

wherein all the symbols are the same meaning as hereinbefore defined, to hydrogenation (including a series of reactions subjecting a compound of the formula (Ib-1) to methylesterification, and to hydrogenation, followed by hydrolysis of the ester bond, for the convenience of purification),

(vi) the amidation or thioamidation of a compound of the formula (VIII):



(VIII)

wherein all the symbols are the same meaning as hereinbefore defined, with a compound of the formula (c):

$$R^6CO_2H \qquad (c)$$

wherein R^6 is the same meaning as hereinbefore defined, or with a compound of the formula (d):

$$R^4R^5N\text{-}L\text{-}CO_2H \qquad (d)$$

wherein all the symbols are the same meaning as herein before defined, or with a compound of the formula (e):

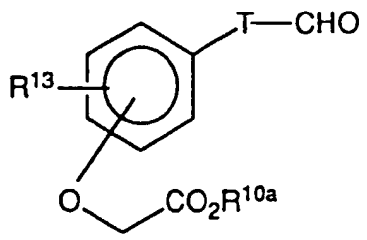
$$R^4\text{-}N{=}C{=}S \qquad (e)$$

wherein R^4 is the same meaning as hereinbefore defined, or with a compound of the formula (f):

$$R^6SO_2Cl \qquad (f)$$

wherein R^6 is the same meaning as hereinbefore defined,

(vii) the reaction of a compound of the formula (VII):



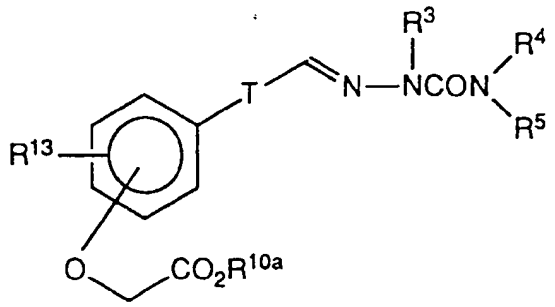
(VII)

wherein all the symbols are the same meaning as hereinbefore defined, with a compound of the formula (g):

$$H_2N\text{-}NR^3\text{-}CONR^4R^5 \quad (g)$$

wherein all the symbols are the same meaning as hereinbefore defined,

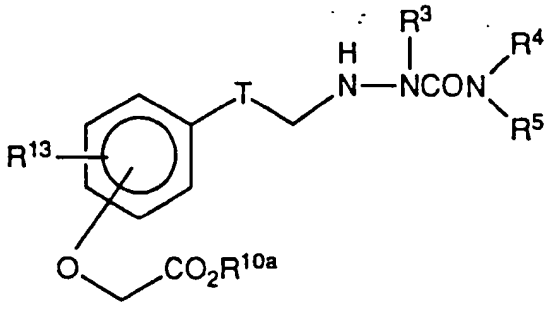
(viii) subjecting a compound obtained by reaction (vii) of the formula (Ia-5):



(Ia-5)

wherein all the symbols are the same meaning as hereinbefore defined, to reduction,

(ix) the reaction of a compound obtained by reaction (viii) of the formula (Ia-6):



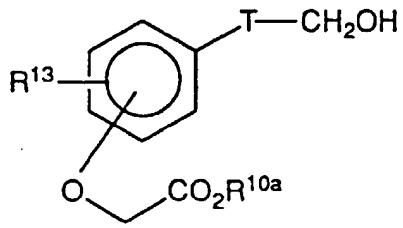
(Ia-6)

wherein all the symbols are the same meaning as hereinbefore defined, with a compound of the formula (h):

$$R^{3a}\text{-}I \quad (h)$$

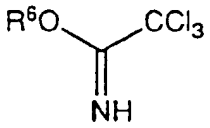
wherein R^{3a} is C1-6 alkyl or phenyl,

(x) the reaction of a compound of the formula (II):



(II)

wherein all the symbols are the same meaning as hereinbefore defined, with a compound of the formula (i):



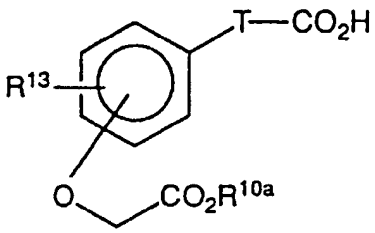
(i)

wherein R^6 is the same meaning as hereinbefore defined, or with a compound of the formula (s):

$$R^6X \qquad (s)$$

wherein X is halogen and R^6 is the same meaning as hereinbefore defined,

(xi) the esterification of a compound of the formula (IV):



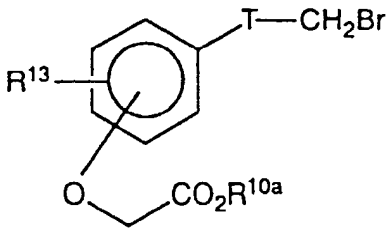
(IV)

wherein all the symbols are the same meaning as hereinbefore defined, with a compound of the formula (j):

$$R^6OH \qquad (j)$$

wherein R^6 is the same meaning as hereinbefore defined,

(xii) the reaction of a compound of the formula (IX):



(IX)

wherein all the symbols are the same meaning as hereinbefore defined,
with a compound of the formula (q):

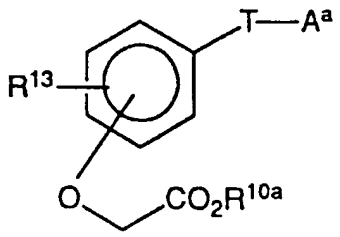
$$HO{\sim}N{=}CR^7R^8 \qquad (q)$$

wherein all the symbols are the same meaning a hereinbefore defined, or with a compound of the formula (r):

$$HO\text{-}NH\text{-}CHR^7R^8 \qquad (r)$$

wherein all the symbols are the same meaning as hereinbefore defined,

(xiii) the hydrolysis of a compound obtained by hereinbefore reaction (i), (ii), (iii), (vi), (vii), (viii), (ix), (x), (xi) or (xii) of the formula (Ia):



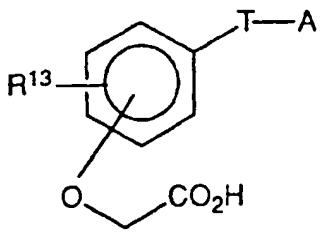
(Ia)

wherein

A^a is
i) $-CR^1{=}N{\sim}OR^2$,
ii) $-CHR^1\text{-}NH\text{-}OR^2$,
iii) -COE,
iv) $-CH_2NR^3\text{-}Y$,
v) $-CH{=}N\text{-}NR^3\text{-}CONR^4R^5$,
vi) $-CH_2\text{-}NH\text{-}NR^3\text{-}CONR^4R^5$,
vii) $-CH_2\text{-}NR^{3a}\text{-}NR^3\text{-}CONR^4R^5$,
viii) $-CH_2OR^6$,
ix) $-CO_2R^6$,
x) $-CH_2\text{-}O{\sim}N{=}CR^7R^8$ or
xi) $-CH_2\text{-}O\text{-}NHCHR^7R^8$,

and the other symbols are the same meaning as hereinbefore defined,

(xiv) the esterification of a compound obtained by hereinbefore reaction (iv) or (v) of the formula (Ib):



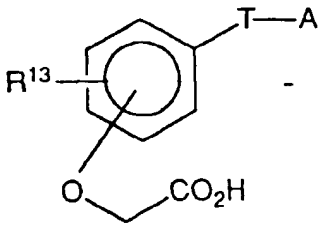
(Ib)

wherein all the symbols are the same meaning as hereinbefore defined, with a compound formula (o):

$$R^{10b}OH \qquad (o)$$

wherein R^{10b} is C1-12 alkyl,

(xv) the amidation of a compound obtained hereinbefore reaction (iv) or (v) of the formula (Ib):



(Ib)

wherein all the symbols are the same meaning as hereinbefore defined,
with a compound formula (p):

$$R^{11}R^{12}NH \qquad (p)$$

wherein all the symbols are the same meaning as hereinbefore defined, or

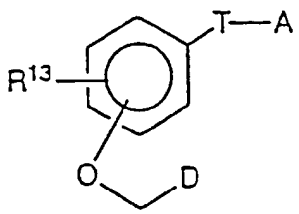
(xvi) the conversion of a phenoxyacetic acid of the fomula (I) into the corresponding salt or acid addtion salt thereof by known method, if desired.

(14) A pharmaceutical composition which comprises, as active ingredient, an effective amount of a phenoxyacetic acid derivative of the formula (I) depicted in claim 1 or a non-toxic salt thereof, or a non-toxic acid addtion salt thereof, with a pharmaceutical carrier or coating.

(15) A phenoxyacetic acid derivative of the formula (I) depicted in claim 1 or a non-toxic salt thereof, or a non-toxic acid addtion salt thereof for use in the manufacture of pharmaceutical composition for the prevention and/or the treatment of thrombsis, arteriosclerosis, ischemic heart diseases, gastric ulcer or hypertension.

Patentansprüche

1. Phenoxyessigsäurederivate der Formel (I);



(I)

worin bedeuten:

A	i) $-CR^1=N-OR^2$, ii) $-CHR^1-NH-OR^2$, iii) - COE, iv) $- SO_2E$, v) $- CH_2-NR^3-Y$, vi) $-Z-NR^3-CONR^4R^5$, vii) $-CH_2-OR^6$, viii) $-CO_2R^6$, ix) $-CH_2-O-N=CR^7R^8$ oder x) $-CH_2O-NHCHR^7R^8$,
T	i) eine Einfachbindung, ii) C1-6-Alkylen, iii) C2-6-Alkenylen oder iv) $-O-(CH_2)_s-$;
D	i) $- CO_2R^{10}$ oder ii) $- CONR^{11}R^{12}$;
E	i) $- NR^4R^5$, ii) $-NR^3OR^6$, iii) $-NR^3-NR^4R^5$ oder iv) $-NR^3-N=CR^4R^5$;
Y	i) $-COR^6$, ii) $-CO-L-NR^4R^5$, iii) - CS-NHR^4 oder iv) $- SO_2R^6$;
Z	i) - CH=N- oder ii) $- CH_2-NR^3-$;
L	eine Einfachbindung oder C1-4-Alkylen;
R^1	Wasserstoff, C1-6-Alkyl oder Phenyl;
R^2	i) C1-8-Alkyl, ein- oder zweifach substituiert durch Phenyl, einen 4-7-gliedrigen monocyclischen Heteroring mit einem Stickstoff oder C4-7-Cycloalkyl, ii) einen kondensierten tricyclischen 010-15-Kohlenwasserstoffring oder iii) C1-15-Alkyl;
R^3	Wasserstoff, C1-6-Alkyl oder Phenyl;
R^4 und R^5 unabhängig voneinander jeweils	i) Wasserstoff, ii) Phenyl,

	iii) einen 4-7-gliedrigen monocyclischen Heteroring mit einem Stickstoff oder iv) C1-4-Alkyl, ein- oder zweifach substituiert durch Phenyl oder einen 4-7-gliedrigen monocyclischen Heteroring mit einem Stickstoff;
R^6	i) Phenyl, ii) einen 4-7-gliedrigen monocyclischen Heteroring mit einem Stickstoff oder iii) C1-4-Alkyl, ein- bis dreifach substituiert durch Phenyl oder einen 4-7-gliedrigen monocyclischen Heteroring mit einem Stickstoff;
R^7	i) Wasserstoff, ii) C1-8-Alkyl, iii) Phenyl oder C4-7-Cycloalkyl, iv) einen 4-7-gliedrigen monocyclischen Heteroring mit einem Stickstoff oder v) C1-4-Alkyl, ein- oder zweifach substituiert durch Phenyl, C4-7-Cycloalkyl oder einen 4-7-gliedrigen monocyclischen Heteroring mit einem Stickstoff;
R^8	i) C1-8-Alkyl, ii) Phenyl oder C4-7-Cycloalkyl, iii) einen 4-7-gliedrigen monocyclischen Heteroring mit einem Stickstoff oder iv) C1-4-Alkyl, ein- oder zweifach substituiert durch Phenyl, C4-7-Cycloalkyl oder einen 4-7-gliedrigen monocyclischen Heteroring mit einem Stickstoff;
R^{10}	Wasserstoff oder Cl-12-Alkyl;
R^{11} und R^{12}	unabhängig voneinander jeweils Wasserstoff oder C1-4-Alkyl oder
R^{11} und R^{12}	zusammen mit dem an R^{11} und R^{12} gebundenen Stickstoff den Rest einer Aminosäure;
R^{13}	Wasserstoff, C1-4-Alkyl, C1-4-Alkoxy oder Nitro;
s =	2 bis 4;

wobei die Ringe von R^1, R^2, R^3, R^4, R^5, R^6, R^7 und R^8 auch ein- bis dreifach durch C1-C4-Alkyl, C1-C4-Alkoxy, Halogen, Nitro oder Trihalogenmethyl substituiert sein können;
wobei gilt, daß

1) wenn A für $-SO_2E$ mit E in der zuvor angegebenen Bedeutung steht, T keine Einfachbindung oder C1-Alkylen (Methylen) darstellt;
2) die Verbindungen mit A gleich -CONH-Phenyl (wobei Phenyl durch 1-3 C1-4-Alkyl, C1-4-Alkoxy, Halogen oder NO_2 substituiert sein kann) ausgeschlossen sind, sowie deren nichttoxische Salze und nichtoxische Säureadditionssalze.

2. Verbindung nach Anspruch 1, wobei D für Carboxy steht.

3. Verbindung nach Anspruch 1, wobei D für C1-12-Alkoxycarbonyl steht.

4. Verbindung nach Anspruch 1, wobei D für $CONR^{11}R^{12}$ mit R^{11} und R^{12} in der in Anspruch 1 angegebenen Bedeutung steht.

5. Verbindung nach Anspruch 1, wobei

A für i) $-CR^1=N-OR^2$,

ii) $-CHR^1-NH-OR^2$,
ix) $-CH_2-O-N=CR^7R^8$ oder
x) $-CH_2-O-NHCHR^7R^8$

mit sämtlichen Symbolen in der in Anspruch 1 angegebenen Bedeutung steht.

6. Verbindung nach Anspruch 1, wobei

A für iii) -COE,
iv) $-SO_2E$,
v) $-CH_2NR^3-Y$ oder
vi) $-Z-NR^3-CONR^4R^5$

mit sämtlichen Symbolen in der in Anspruch 1 angegebenen Bedeutung steht.

7. Verbindung nach Anspruch 1, wobei

A für vii) $-CH_2OR^6$

mit R^6 in der in Anspruch 1 angegebenen Bedeutung steht.

8. Verbindung nach Anspruch 1, wobei

A für viii) $-CO_2R^6$

mit R^6 in der in Anspruch 1 angegebenen Bedeutung steht.

9. Verbindung nach Anspruch 5, nämlich

3-(4-Diphenylmethyloxyiminobutyl)phenoxyessigsäure,
4-(3-Diphenylmethyloxyiminopropyl)phenoxyessigsäure,
4-(4-Diphenylmethyloxyiminobutyl)phenoxyessigsäure,
3-(3-Diphenylmethyloxyiminopropyl)phenoxyessigsäure,
3-(4-Diphenylmethyloxyiminoheptyl)phenoxyessigsäure,
3-(4-Diphenylmethyloxyaminoheptyl)phenoxyessigsäure,
3-[2-[2-Phenyl-2-(3-pyridyl)ethyl]oxyiminoethyl]phenoxyessigsäure,
3-[2-[2-Cyclohexyl-2-phenylethyl)oxyiminoethyl]phenoxyessigsäure,
3-[2-[2-(Fluoren-9-yl)ethyl]oxyiminoethyl]phenoxyessigsäure,
3-[2-(2-Phenyldecyl)oxyiminoethyl]phenoxyessigsäure,
3-[2-Di(3-pyridyl)methyloxyiminoethyl]phenoxyessigsäure,
3-[4-Methyl-4-(1-phenyl-1-(3-pyridyl)methyloxyimino)butyl]phenoxyessigsäure,
3-[2-[1-Phenyl-1-(3-pyridyl)methylidenaminooxy]ethyl]phenoxyessigsäure,
3-[3-[1-Phenyl-1-(3-pyridyl)methylidenaminooxy]propyl]phenoxyessigsäure,
2-[3-[1-Phenyl-1-(3-pyridyl)methylidenaminooxy]propyl]phenoxyessigsäure,
2-[4-[1-Phenyl-1-(3-pyridyl)methylidenaminooxy]butyl]phenoxyessigsäure,
2-[5-[1-Phenyl-1-(3-pyridyl)methylidenaminooxy]pentyl]phenoxyessigsäure,
3-[3-[1-Phenyl-1-(3-pyridyl)methylidenaminooxy]-1-propenyl]phenoxyessigsäure,
3-[2-[1-Phenyl-1-(3-pyridyl)methylidenaminooxy]ethyloxy]phenoxyessigsäure,
3-[3-[Di(3-pyridyl)methylidenaminooxy]propyl]phenoxyessigsäure,
3-[3-[1-Cyclohexyl-1-phenylmethylidenaminooxy]propyl]phenoxyessigsäure,
2-Methyl-3-[3-[1-phenyl-1-(3-pyridyl)methylidenaminooxy]propyl]phenoxyessigsäure,
3-[3-[1-Phenyl-1-(3-pyridyl)methylaminooxy]propyl]phenoxyessigsäure,

sowie deren Methylester, Octylester, Acetamide oder Amide mit Glycin.

10. Verbindung nach Anspruch 6, nämlich

3-(3,3-Diphenylpropylaminocarbonylmethyl)phenoxyessigsäure,

3-(N-Benzyl-N-phenylaminocarbonylmethyl)phenoxyessigsäure,
3-(N,N-Dibenzylaminocarbonylmethyl)phenoxyessigsäure, 3-(N-Benzylaminocarbonylmethyl)phenoxyessigsäure,
3-(Diphenylmethylaminocarbonylmethyl)phenoxyessigsäure,
3-[(N,N-Diphenylamino)aminocarbonylmethyl]phenoxyessigsäure,
3-(1,2-Diphenylethylaminocarbonylmethyl)phenoxyessigsäure,
3-(2,2-Diphenylethylaminocarbonylmethyl)phenoxyessigsäure,
3-(Diphenylmethyloxyaminocarbonylmethyl)phenoxyessigsäure,
3-[(1,1-Diphenylmethylidenamino)aminocarbonylmethyl]phenoxyessigsäure,
3-[3-(3,3-Diphenylpropylaminocarbonyl)propyl]phenoxyessigsäure,
3-[3-(N-Benzyl-N-phenylaminocarbonyl)propyl]phenoxyessigsäure,
3-[3-(N,N-Dibenzylaminocarbonyl)propyl]phenoxyessigsäure,
3-(3-Benzylaminocarbonylpropyl)phenoxyessigsäure,
3-(3-Diphenylmethylaminocarbonylpropyl)phenoxyessigsäure,
3-[3-[(N,N-Diphenylamino)aminocarbonyl]propyl]phenoxyessigsäure,
3-[3 -(1,2-Diphenylethylaminocarbonyl)propyl]phenoxyessigsäure,
3-[3-(2,2-Diphenylethylaminocarbonyl)propyl]phenoxyessigsäure,
3-(3-Diphenylmethyloxyaminocarbonylpropyl)phenoxyessigsäure,
3-[3-[(1,1-Diphenylmethylidenamino)aminocarbonyl]propyl]phenoxyessigsäure,
3-[2-(3,3-Diphenylpropylaminocarbonyl)ethyl]phenoxyessigsäure,
3-[2-(N-Benzyl-N-phenylaminocarbonyl)ethyl]phenoxyessigsäure,
3-[2-(N,N-Dibenzylaminocarbonyl)ethyl]phenoxyessigsäure,
3-(2-Benzylaminocarbonylethyl)phenoxyessigsäure,
3-(2-Diphenylmethylaminocarbonylethyl)phenoxyessigsäure,
3-[2-[(N,N-Diphenylamino)aminocarbonyl]ethyl]phenoxyessigsäure,
3-[2-(1,2-Diphenylethylaminocarbonyl)ethyl]phenoxyessigsäure,
3-[2-(2,2-Diphenylethylaminocarbonyl)ethyl]phenoxyessigsäure,
3-(2-Diphenylmethyloxyaminocarbonylethyl)phenoxyessigsäure,
3-[2-[(1,1-Diphenylmethylidenamino)aminocarbonyl]ethyl]phenoxyessigsäure,
3-(4-Diphenylaminosulfonyl-3-butenyl)phenoxyessigsäure,
3-(4-Diphenylaminosulfonylbutyl)phenoxyessigsäure,
4-(2-Benzoylaminoethyl)phenoxyessigsäure,
4-[2-(N,N-Diphenylaminocarbonylamino)ethyl]phenoxyessigsäure,
4-[2-(N,N-Diphenylaminomethylcarbonylamino)ethyl]phenoxyessigsäure,
4-(2-Phenylaminothiocarbonylaminoethyl)phenoxyessigsäure,
4-(2-Phenylsulfonylaminoethyl)phenoxyessigsäure,
4-[2-(N,N-Diphenylaminocarbonylaminoimino)ethyl]phenoxyessigsäure,
3-(3-Diphenylmethyloxyaminosulfonylpropyl)phenoxyessigsäure,
3-[3-[(N,N-Diphenylamino)aminosulfonyl]propyl]phenoxyessigsäure,
3-[3-[(1,1-Diphenylmethylidenamino)aminosulfonyl]propyl]phenoxyessigsäure,
4-[2-[(N,N-Diphenylaminocarbonylamino)amino]ethyl]phenoxyessigsäure,

oder deren Methylester, Octylester, Acetamide oder Amide mit Glycin.

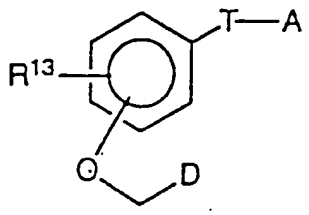
11. Verbindung nach Anspruch 7, nämlich

3-(4-Diphenylmethyloxybutyl)phenoxyessigsäure,
3-(3-Diphenylmethyloxypropyl)phenoxyessigsäure,
3-(4-Triphenylmethoxybutyl)phenoxyessigsäure,

oder deren Methylester, Octylester, Acetamide oder Amide mit Glycin.

12. Verbindung nach Anspruch 8, nämlich
3-(3-Diphenylmethyloxycarbonylpropyl)phenoxyessigsäure, oder deren Methylester, Octylester, Acetamid oder Amid mit Glycin.

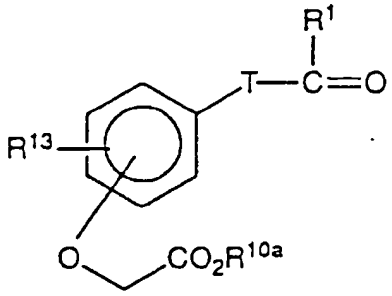
13. Verfahren zur Herstellung von Phenoxyessigsäurederivaten der Formel (I):



(I)

worin sämtliche Symbole die zuvor in Anspruch 1 angegebene Bedeutung besitzen, oder von deren Salzen oder Säureadditionssalzen, gekennzeichnet durch:

(i) Umsetzung einer Verbindung der Formel (III):



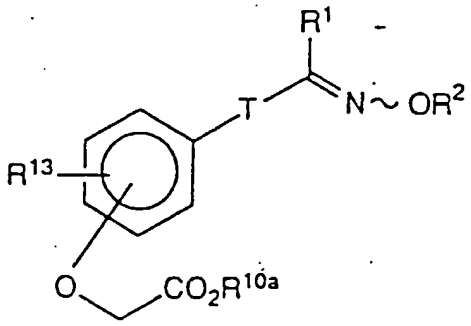
(III)

worin R^{10a} für Methyl oder Ethyl steht und die sonstigen Symbole die zuvor angegebene Bedeutung besitzen, mit einer Verbindung der Formel (a) :

$$R^2ONH_2 \qquad (a)$$

worin R^2 die zuvor angegebene Bedeutung besitzt;

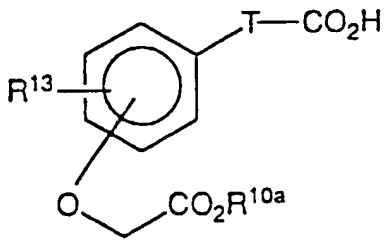
(ii) Reduktion einer bei der Reaktion (i) erhaltenen Verbindung der Formel (Ia-1) :



(Ia-1)

worin sämtliche Symbole die zuvor angegebene Bedeutung besitzen;

(iii) Amidierung einer Verbindung der Formel (IV):



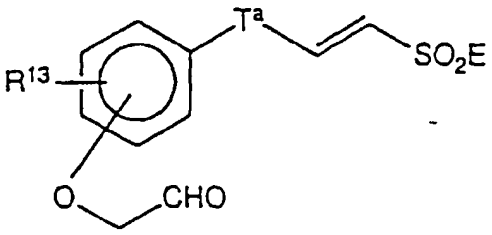
(IV)

worin sämtliche Symbole die zuvor angegebene Bedeutung besitzen,
mit einer Verbindung der Formel (b):

HE (b)

worin E die zuvor angegebene Bedeutung besitzt;

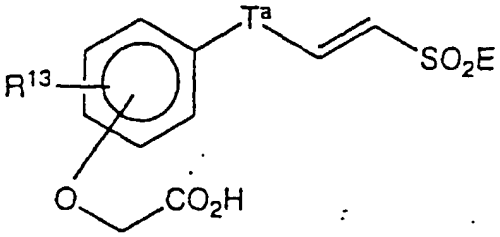
(iv) Jone'sche Oxidation einer Verbindung der Formel (VI) :



(VI)

worin T^a für eine Einfachbindung, C1-4-Alkylen, C2-4-Alkenylen oder -O-$(CH_2)_t$- mit t = 0 bis 2 steht und die sonstigen Symbole die zuvor angegebene Bedeutung besitzen;

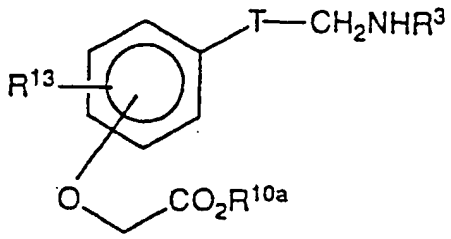
(v) Hydrierung einer bei der Reaktion (iv) erhaltenen Verbindung der Formel (Ib-1)



(Ib-1)

worin sämtliche Symbole die zuvor angegebene Bedeutung besitzen (einschließlich einer Reihe von Reaktionen, bei welchen - zur bequemeren Reinigung - eine Verbindung der Formel (Ib-1) methylverestert und hydriert und danach die Esterbindung hydrolysiert werden);

(vi) Amidierung oder Thioamidierung einer Verbindung der Formel (VIII):



(VIII)

worin sämtliche Symbole die zuvor angegebene Bedeutung besitzen,
mit einer Verbindung der Formel (c):

$$R^6CO_2H \qquad (c)$$

worin R^6 die zuvor angegebene Bedeutung besitzt, oder mit einer Verbindung der Formel (d):

$$R^4R^5N\text{-}L\text{-}CO_2H \qquad (d)$$

worin sämtliche Symbole die zuvor angegebene Bedeutung besitzen, oder
mit einer Verbindung der Formel (e)

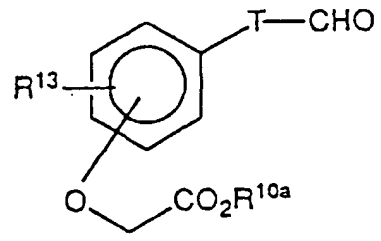
$$R^4\text{-}N{=}C{=}S \qquad (e)$$

worin R^4 die zuvor angegebene Bedeutung besitzt, oder mit einer Verbindung der Formel (f) :

$$R^6SO_2Cl \qquad (f)$$

worin R^6 die zuvor angegebene Bedeutung besitzt;

(vii) Reaktion einer Verbindung der Formel (VII):



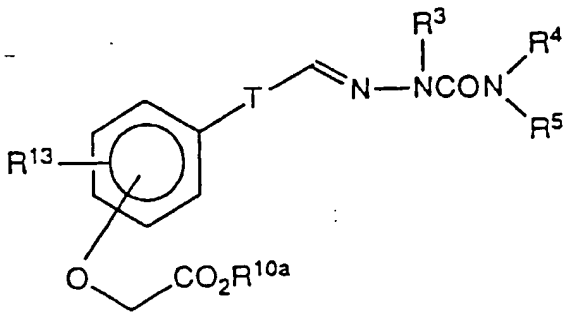
(VII)

worin sämtliche Symbole die zuvor angegebene Bedeutung besitzen,
mit einer Verbindung der Formel (g):

$$H_2N\text{-}NR^3\text{-}CONR^4R^5 \qquad (g)$$

worin sämtliche Symbole die zuvor angegebene Bedeutung besitzen;

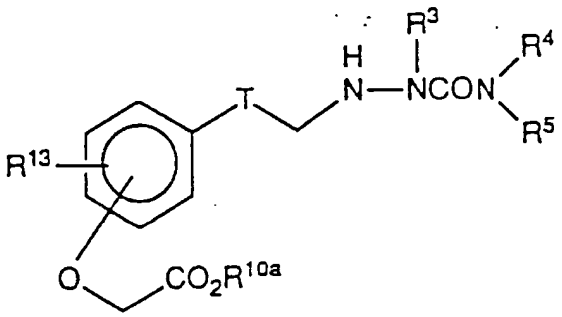
(viii) Reduktion einer bei der Reaktion (vii) erhaltenen Verbindung der Formel (Ia-5):



(Ia-5)

worin sämtliche Symbole die zuvor angegebene Bedeutung besitzen;

(ix) Reaktion einer bei der Reaktion (viii) erhaltenen Verbindung der Formel (Ia-6):



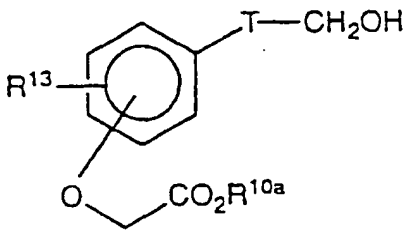
(Ia-6)

worin sämtliche Symbole die zuvor angegebene Bedeutung besitzen,
mit einer Verbindung der Formel (h):

$$R^{3a}I \qquad (h)$$

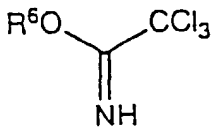
worin für R^{3a} C1-6-Alkyl oder Phenyl steht,

(x) Reaktion einer Verbindung der Formel (II):



(II)

worin sämtliche Symbole die zuvor angegebene Bedeutung besitzen,
mit einer Verbindung der Formel (i) :



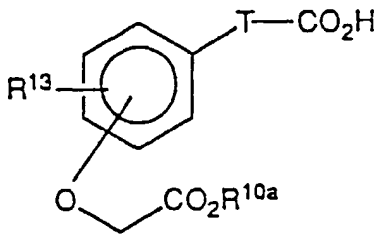
(i)

worin R^6 die zuvor angegebene Bedeutung besitzt, oder mit einer Verbindung der Formel (s):

$$R^6X \qquad (s)$$

worin X für Halogen steht und R^6 die zuvor angegebene Bedeutung besitzt,

(xi) Veresterung einer Verbindung der Formel (IV):



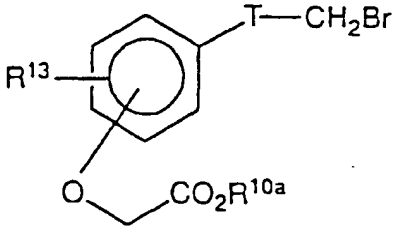
(IV)

worin sämtliche Symbole die zuvor angegebene Bedeutung besitzen,
mit einer Verbindung der Formel (j) :

$$R^6OH \qquad (j)$$

worin R^6 die zuvor angegebene Bedeutung besitzt,

(xii) Reaktion einer Verbindung der Formel (IX):



(IX)

worin sämtliche Symbole die zuvor angegebene Bedeutung besitzen,
mit einer Verbindung der Formel (q):

$$HO\text{-}N{=}CR^7R^8 \qquad (q)$$

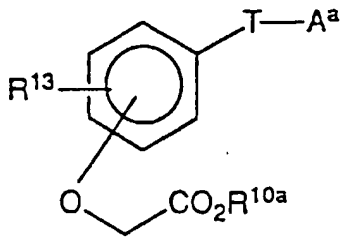
worin sämtliche Symbole die zuvor angegebene Bedeutung besitzen, oder

mit einer Verbindung der Formel (r) :

$$HO\text{-}NH\text{-}CHR^7R^8 \qquad (r)$$

worin sämtliche Symbole die zuvor angegebene Bedeutung besitzen;

(xiii) Hydrolyse einer bei einer der vorhergehenden Reaktionen (i), (ii), (iii), (vi), (vii), (viii), (ix), (x), (xi) oder (xii) erhaltenen Verbindung der Formel (Ia):

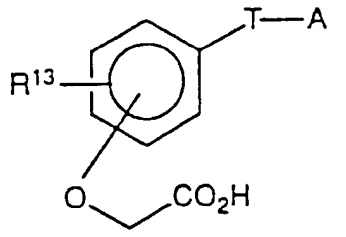


(Ia)

worin A^a für i) $-CR^1=N-OR^2$,
ii) $-CHR^1-NH-OR^2$,
iii) -COE,
iv) $-CH_2NR^3-Y$,
v) $-CH=N-NR^3-CONR^4R^5$,
vi) $-CH_2-NH-NR^3-CONR^4R^5$,
vii) $-CH_2-NR^{3a}-NR^3-CONR^4R^5$,
viii) $-CH_2OR^6$,
ix) $-CO_2R^6$,
x) $-CH_2-O-N=CR^7R^8$ oder
xi) $-CH_2-O-NHCHR^7R^8$

steht und die sonstigen Symbole die zuvor angegebene Bedeutung besitzen;

(xiv) Veresterung einer bei der vorhergehenden Reaktion (iv) oder (v) erhaltenen Verbindung der Formel (Ib):



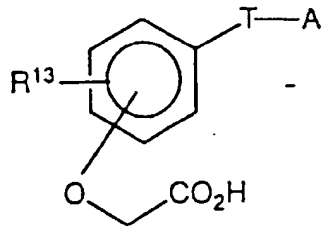
(Ib)

worin sämtliche Symbole die zuvor angegebene Bedeutung besitzen,
mit einer Verbindung der Formel (o) :

$$R^{10b}OH \qquad (o)$$

worin R^{10b} für C1-12-Alkyl steht;

(xv) Amidierung einer bei der vorhergehenden Reaktion (iv) oder (v) erhaltenen Verbindung der Formel (Ib):



(Ib)

worin sämtliche Symbole die zuvor angegebene Bedeutung besitzen,
mit einer Verbindung der Formel (p) :

$$R^{11}R^{12}NH \qquad (p)$$

worin sämtliche Symbole die zuvor angegebene Bedeutung besitzen, oder

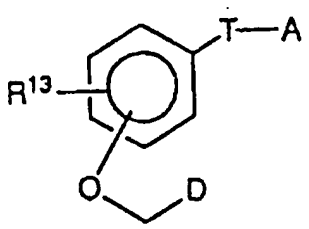
(xvi) gewünschtenfalls Umwandlung einer Phenoxyessigsäure der Formel (I) in das entsprechende Salz oder Säureadditionssalz nach einem bekannten Verfahren.

14. Arzneimittelzubereitung, enthaltend als aktiven Bestandteil eine wirksame Menge eines Phenoxyessigsäurederivats der in Anspruch 1 dargestellten Formel (I) oder eines nichttoxischen Salzes desselben oder eines nichttoxischen Säureadditionssalzes desselben zusammen mit einem pharmazeutischen Träger oder Überzug.

15. Phenoxyessigsäurederivat der in Anspruch 1 dargestellten Formel (I) oder ein nichttoxisches Salz desselben oder ein nichttoxisches Säureadditionssalz desselben zur Verwendung bei der Herstellung einer Arzneimittelzubereitung zur Verhinderung und/oder Behandlung von Thrombose, Arteriosklerose, ischämischen Herzkrankheiten, Magengeschwür oder Bluthochdruck.

Revendications

1. Dérivé d'acide phénoxyacétique de formule (I) :



(I)

dans laquelle A représente
- i) $-CR^1=N\sim OR^2$
- ii) $-CHR^1-NH-OR^2$
- iii) -COE,
- iv) $-SO_2E$,
- v) $-CH_2-NR^3-Y$
- vi) $-Z-NR^3-CONR^4R^5$,
- vii) $-CH_2-R^6$,
- viii) $-CO_2R^6$,
- ix) $-CH_2-O\sim N=CR^7R^8$ ou
- x) $-CH_2-O-NHCHR^7R^8$,

T représente
- i) une simple liaison,
- ii) un groupe alkylène en C_{1-6},

iii) un groupe alcénylène en C_{2-6}, ou
iv) $-O-(CH_2)s^-$;

D représente
i) $-CO_2R^{10}$ ou
ii) $-CONR^{11}R^{12}$;

E représente
i) $-NR^4R^5$
ii) $-NR^3OR^6$,
iii) $-NR^3-NR^4R^5$ ou
iv) $-NR^3-N=CR^4R^5$;

Y représente
i) $-COR^6$,
ii) $-CO-L-NR^4R^5$,
iii) $-CS-NHR^4$ ou
iv) $-SO_2R^6$;

Z représente
i) -CH=N ou
ii) $-CH_2-NR^{3-}$;

L représente une simple liaison ou un groupe alkylène en C_{1-4};

R^1 représente un atome d'hydrogène, un groupe alkyle en C_{1-6} ou un groupe phényle ;

R^2 représente
i) un groupe alkyle en C_{1-8} substitué par un ou deux groupes phényle, hétérocycles monocycliques à 4 à 7 membres contenant un atome ou groupes cycloalkyle en C_{4-7},
ii) un noyau tricyclique condensé hydrocarboné en C_{10-15} ou
iii) un groupe alkyle en C_{1-15} ;

R^3 représente un atome d'hydrogène, un groupe alkyle en C_{1-6} ou un groupe phényle ;

R^4 et R^5 représentent chacun indépendamment,i) un atome d'hydrogène,
ii) un groupe phényle,
iii) un hétérocycle monocyclique à 4-7 membres contenant un atome d'azote ou
iv) un groupe alkyle en C_{1-4} substitué par un ou deux groupes phényle ou hétérocycles monocycliques à 4-7 membres contenant un atome d'azote,

R^6 représente
i) un groupe phényle,
ii) un hétérocycle monocyclique à 4-7 membres contenant un atome d'azote, ou
iii) un groupe alkyle en C_{1-4} substitué par un à trois groupes phényle ou hétérocycles monocycliques à 4-7 membres contenant un atome d'azote ;

R^7 représente
i) un atome d'hydrogène,
ii) un groupe alkyle en C_{1-8},
iii) un groupe phényle ou un groupe cycloalkyle en C_{4-7},
iv) un hétérocycle monocyclique à 4-7 membres contenant un atome d'azote ou
v) un groupe alkyle en C_{1-4} substitué par un ou groupes phényle, cycloalkyle en C_{4-7} ou hétérocycles monocycliques à 4-7 membres contenant un atome d'azote ;

R^8 représente
i) un groupe alkyle en C_{1-8},
ii) un groupe phényle ou un groupe cycloalkyle en C_{4-7},
iii) un hétérocycle monocyclique à 4-7 membres contenant un atome d'azote, ou
iv) un groupe alkyle en C_{1-4} substitué par un ou deux groupes phényle, cycloalkyle en C_{4-7} ou hétérocycles monocycliques à 4-7

membres contenant un atome d'azote ; R^{10} représente un atome d'hydrogène ou un groupe alkyle en C_{1-12} ;

R^{11} et R^{12} représentent chacun, indépendamment,un atome d'hydrogène ou un groupe alkyle en C_{1-4} ou

R^{11} et R^{12}, pris ensembles avec une liaison azote entre R^{11} et R^{12} représentent le résidu d'un acide aminé ;

R^{13} représente un atome d'hydrogène, un groupe alkyle en C_{1-4}, un groupe alcoxy en C_{1-4} ou un groupe nitro ;

s vaut 2 à 4 ;

et les cycles représentés par R^1, R^2, R^3, R^4, R^5, R^6, R^7 et R^8 peuvent également être substitués par un à trois groupes alkyle en C_{1-4}, alcoxy en C_{1-4}, atomes d'halogène, groupes nitro ou trihalogénométhyle;
à la condition que,

1) lorsque A représente $-SO_2E$, dans lequel E a la signification définie ci-dessus, T ne représente pas une simple liaison et un groupe alkylène en C_1 (méthylène),
2) les composés dans lesquels A représente -CONH-phényle (le groupe phényle pouvant être substitué par 1 à 3 groupes alkyle en C_{1-4}, alcoxy en C_{1-4}, atomes d'halogène ou NO_2) sont exclus, et ses sels non toxiques et ses sels par addition d'acide non toxiques.

2. Composé conforme à la revendication 1, dans lequel D représente un groupe carboxy.

3. Composé conforme à la revendication 1, dans lequel D représente un groupe alcoxycarbonyle en C_{1-12}.

4. Composé conforme à la revendication 1, dans lequel D représente $CONR^{11}R^{12}$ dans lequel R^{11} et R^{12} ont la signification définie dans la revendication 1.

5. Composé conforme à la revendication 1 dans lequel

A représente
i) $-CR^1=N\sim OR^2$,
ii) $-CHR^1-NH-OR^2$,
ix) $-CH_2-O\sim N=CR^7R^8$ ou
x) $-CH_2-O-NHCHR^7R^8$

dans lesquels tous les symboles ont les significations définies dans la revendication 1.

6. Composé conforme à la revendication 1, dans lequel

A représente
iii) -COE,
iv) $-SO_2E$
v) $-CH_2N^3-Y$ ou
vi) $-Z-NR^3-CONR^4R^5$

dans lesquels tous les symboles ont les significations définies dans le revendication 1.

7. Composé conforme à la revendication 1, dans lequel

A représente vii) $-CH_2OR^6$

dans laquelle R^6 a la signification définie dans la revendication 1.

8. Composé conforme à la revendication 1, dans lequel

A représente viii) $-CO_2R^6$

dans laquelle R^6 a la signification définie dans la revendication 1.

9. Composé conforme à la revendication 5, qui est

l'acide 3-(4-diphénylméthyloxyiminobutyl)phénoxyacétique,
l'acide 4-(3-diphénylméthyloxyiminopropyl)phénoxyacétique,
l'acide 4-(4-diphénylméthyloxyiminobutyl)phénoxyacétique,
l'acide 3-(3-diphénylméthyloxyiminopropyl)phénoxyacétique,
l'acide 3-(4-diphénylméthyloxyiminoheptyl)phénoxyacétique,
l'acide 3-(4-diphénylméthyloxyaminoheptyl)phénoxyacétique,
l'acide 3-[2-(2-phényl-2-(3-pyridyl)éthyl]oxyiminoéthyl]phénoxyacétique,
l'acide 3-[2-(2-cyclohexyl-2-phényléthyl)oxyiminoéthyl]phénoxyacétique,
l'acide 3-[2-(2-(fluorène-9-yl)éthyl]oxyiminoéthyl]phénoxyacétique,
l'acide 3-[2-(2-phényldécyl)oxyiminoéthyl]phénoxyacétique, l'acide 3-[2-di(3-pyridyl)méthyloxyiminoéthyl] phénoxyacétique,
l'acide 3-[4-méthyl-4-(1-phényl-1-(3-pyridyl)méthyloxyimino)butyl]phénoxyacétique,
l'acide 3-[2-[1-phényl-1-(3-pyridyl)méthylidènaminooxy]éthyl]phénoxyacétique,
l'acide 3-[3-[1-phényl-1-(3-pyridyl)méthylidènaminooxy]propyl]phénoxyacétique,
l'acide 2-[3-[1-phényl-1-(3-pyridyl)méthyfidènammooxy]propyl]phénoxyacétique,
l'acide 2-[4-[1-phényl-1-(3-pyridyl)méthyfidènaminooxy]butyl]phénoxyacétique,
l'acide 2-[5-[1-phényl-1-(3-pyridyl)méthylidènaminooxy]pentyl]phénoxyacétique,
l'acide 3-[3-[1-phényl-1-(3-pyridyl)méthylidènaminooxy]-1-propényl]phénoxyacétique,
l'acide 3-[2-[1-phényl-1-(3-pyridyl)méthylidènaminooxy]éthyloxy]phénoxyacétique,
l'acide 3-[3-[di(3-pyridyl)méthylidènaminooxy]propyl]phénoxyacétique,
l'acide 3-[3-[1-cyclohexyl-1-phénylméthylidènamonooxy]propyl]phénoxyacétique,
l'acide 2-méthyl-3-[3-[1-phényl-1-(3-pyridyl) méthylidènaminooxy] propyl] phénoxyacétique,
l'acide 3-[3-[1-phényl-1-(3-pyridyl)méthylaminooxy]propyl]phénoxyacétique,

ou leurs esters méthyliques, ou leurs esters octyliques, ou leurs acétamides, ou leurs amides avec la glycine.

10. Composé conforme à la revendication 6, qui est

l'acide 3-(3,3-diphénylpropylaminocarbonylméthyl)phénoxyacétique,
l'acide 3-(N-benzyl-N-phénylaminocarbonylméthyl)phénoxyacétique,
l'acide 3-(N,N-dibenzylaminocarbonylméthyl)phénoxyacétique,
l'acide 3-(N-benzylaminocarbonylméthyl)phénoxyacétique,
l'acide 3-(diphénylméthylaminocarbonylméthyl)phénoxyacétique,
l'acide 3-[(N,N-diphénylamino)aminocarbonylméthyl)phénoxyacétique,
l'acide 3-(1,2-diphènyléthylaminocarbonylméthyl)phénoxyacétique,
l'acide 3-(2,2-diphényléthylaminocarbonylméthyl)phénoxyacétique,
l'acide 3-(diphénylméthyloxyaminocarbonylméthyl)phénoxyacétique,
l'acide 3-[(1,1-diphénylméthylidènamino)anùnocarbonylméthyl]phénoxyacétique
l'acide 3-[3-(3,3-dîphénylpropylaminocarbonyl) propyl] phénoxyacétique,
l'acide 3-[3-(N-benzyl-N-phénylaminocarbonyl) propyl] phénoxyacétique,
l'acide 3-[3-(N,N-dibenzylaminocarbonyl)propyl]phénoxyacétique,
l'acide 3-(3-benzylaminocarbonylpropyl)phénoxyacéfique,
l'acide 3-(3-diphénylméthylaminocarbonylpropyl)phénoxyacétique,
l'acide 3-[3-[(N,N-diphénylamino)aminocarbonyl]propyl]phénoxyacétique,
l'acide 3-[3-(1,2-diphényléthylaminocarbonyl)propyl]phénoxyacéfique,
l'acide 3-[3-(2,2-diphényléthylaminocarbonyl) propyl] phénoxyacétique,
l'acide 3-(3-diphénylméthyloxyaminocarbonylpropyl)phénoxyacétique,
l'acide 3-[3-[(1,1-diphénylméthylidènamino)aminocarbonyl]-propyl]phénoxyacétique,
l'acide 3-[2-(3,3-diphénylpropylaminocarbonyl)éthyl]phénoxyacétique,
l'acide 3-[2-(N-benzyl-N-phénylaminocarbonyl)éthyl] phénoxyacétique,
l'acide 3-(2-(N,N-dibenzylaminocarbonyl)éthyl)phénoxyacétique,
l'acide 3-(2-benzylaminocarbonyléthyl)phénoxyacétique,
l'acide 3-(2-diphénylméthylaminocarbonyléthyl)phénoxyacétique,
l'acide 3-[2-[(N,N-diphénylamino)aminocarbonyl]éthyl]phénoxyacétique,
l'acide 3-[2-(1,2-diphényléthylaminocarbonyl)éthyl]phénoxyacétique,
l'acide 3-[2-(2,2-diphényléthylaminocarbonyl)éthyl]phénoxyacétique,
l'acide 3-(2-diphénylméthyloxyaminocarbonyléthyl)phénoxyacétique,
l'acide 3-[1-[(1,1-diphénylméthylidènamino)aminocarbonyl]éthyl]phénoxyacétique,

l'acide 3-(4-diphénylaminosulfonyl-3-butényl) phénoxyacétique,
l'acide 3-(4-diphénylaminosulfonylbutyl)phénoxyacétique,
l'acide 4-(2-benzoylaminoéthyl)phénoxyacétique,
l'acide 4-[2-(N,N-diphénylaminocarbonylamino)éthyl] phénoxyacétique,
l'acide 4-[2-(N,N-diphénylaminométhylcarbonylamino)éthyl]phénoxyacétique,
l'acide 4-(2-phénylaminothiocarbonylaminoéthyl)phénoxyacétique,
l'acide 4-(2-phénylsulfonylaminoéthyl)phénoxyacétique,
l'acide 4-[2-(N,N-diphénylaminocarbonylaminoimino)éthyl]phénoxyacétique,
l'acide 3-(3-diphénylméthyloxyaminosulfonylpropyl)phénoxyacétique,
l'acide 3-[3-[(N,N-diphénylamino)aminosulfonyl]propyl]phénoxyacétique,
l'acide 3-[3-(1,1-diphénylméthylidèneamino)aminosulfonyl]propyl]phénoxyacétique,
l'acide 4-[2-[(N,N-diphénylaminocarbonylamino)phénoxyacétique,

ou leurs esters méthyliques, ou leurs esters acryliques, ou leurs acétamides, ou leurs amides avec la glycine.

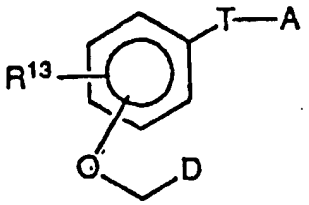
11. Composé conforme à la revendication 7, qui est

l'acide 3-(4-diphénylméthyloxybutyl)phénoxyacétique,
l'acide 3-(3-diphénylméthyloxypropyl)phénoxyacétique,
l'acide 3-(4-triphénylméthoxybutyl)phénoxyacétique,

ou leurs esters méthyliques, ou leurs esters octyliques, ou leurs acétamides, ou leurs amides avec de la glycine.

12. Composé conforme à la revendication 8, qui est
l'acide 3-(3-diphénylméthyloxycarbonylpropyl)phénoxyacétique,
ou son ester méthylique, ou son ester octylique, ou son acétamide, ou son amide avec la glycine.

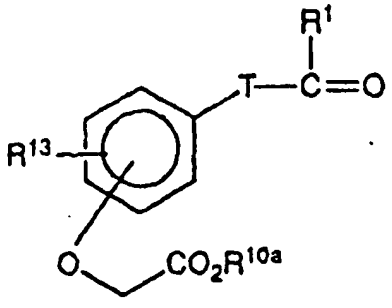
13. Procédé de préparation de dérivés d'acide phénoxyacétique de formule (I) :



(I)

dans laquelle tous les symboles ont les significations définies ci-dessus dans la revendication 1 ou leurs sels ou leurs sels par addition d'acide, qui est caractérisé par les étapes consistant à :

(i) faire réagir un composé de formule (III) :

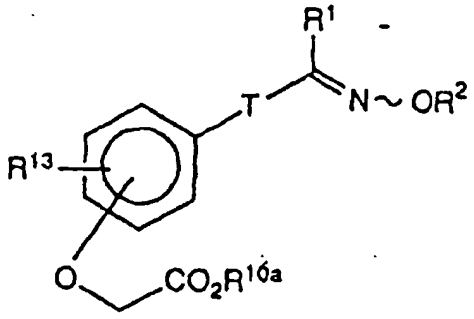


(III)

dans laquelle R^{10a} désigne un groupe méthyle ou éthyle et les autres symboles ont les significations définies ci-dessus, avec un composé de formule (a) :

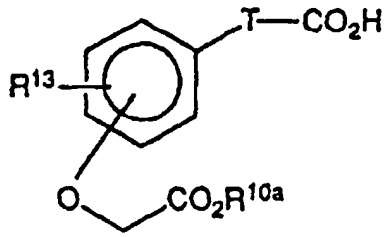
R^2ONH_2 (a)

dans laquelle R^2 a la signification définie ci-dessus,
(ii) soumettre un composé obtenu par la réaction (i) de formule (1a-1) :



(Ia-1)

dans laquelle tous les symboles ont les significations définies ci-dessus, à une réduction,
(iii) effectuer l'amidation d'un composé de formule (IV) :

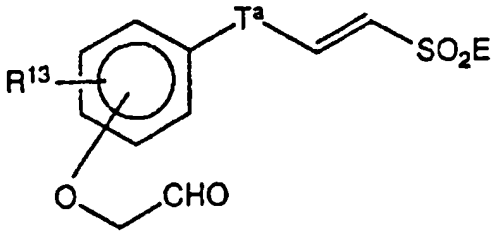


(IV)

dans laquelle tous les symboles ont les significations définies ci-dessus, avec un composé de formule (b) :

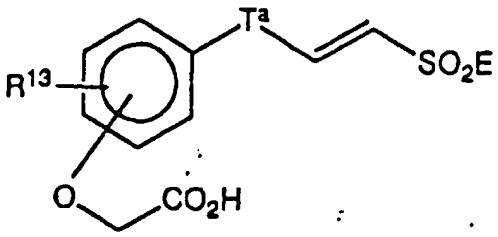
HE (b)

dans laquelle E a la signification définie ci-dessus,
(iv) soumettre un composé de formule (VI) :



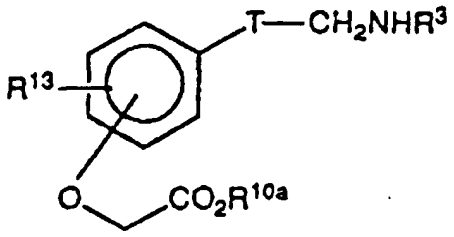
(VI)

dans laquelle T^a représente une simple liaison, un groupe alkylène en C_{1-4}, un groupe alcénylène en C_{2-4}, ou $-O-(CH_2)_t-$ dans laquelle t vaut 0 à 2, et les autres symboles ont les significations définies ci-dessus, à une oxydation de Jone,
(v) soumettre un composé obtenu par la réaction (iv) de formule (Ib-1) :



(Ib-1)

dans laquelle tous les symboles ont les significations définies ci-dessus, à une hydrogénation (incluant une série de réactions soumettant un composé de formule (Ib-1) à une méthylestérification, et à une hydrogénation, suivie d'une hydrolyse de la liaison ester, à des fins pratiques de purification),
(vi) effectuer l'amidation ou la thioamidation d'un composé de formule (VIII) :



(VIII)

dans laquelle tous les symboles ont les significations définies ci-dessus, avec un composé de formule (c) :

$$R^6OC_2H \qquad (c)$$

dans laquelle R^6 a la signification définie ci-dessus, ou avec un composé de formule (d) :

$$R^4R^5N\text{-}L\text{-}CO_2H \qquad (d)$$

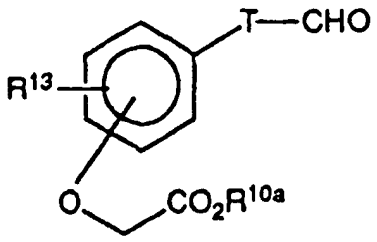
dans laquelle tous les symboles ont les significations définies ci-dessus, ou avec un composé de formule (e) :

$$R^4\text{-}N{=}C{=}S \qquad (e)$$

dans laquelle R^4 a la signification définie ci-dessus, ou avec un composé de formule (f) :

$$R^6SO_2Cl \qquad (f)$$

dans laquelle R^6 a la signification définie ci-dessus :
(vii) faire réagir un composé de formule (VII) :

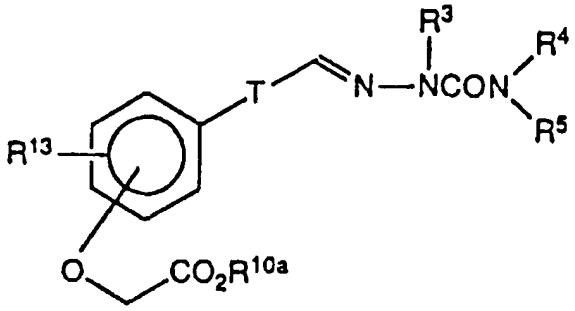


(VII)

dans laquelle tous les symboles ont les significations définies ci-dessus avec un composé de formule (g) :

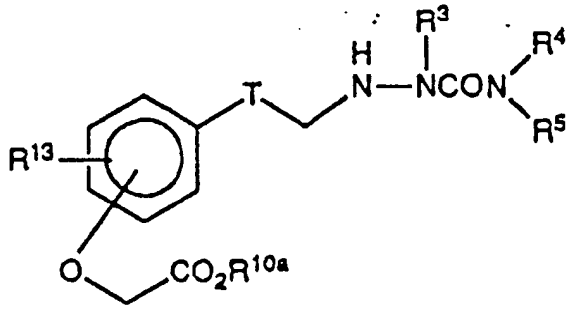
$$H_2N\text{-}NR^3\text{-}CONR^4R^5 \qquad (g)$$

dans laquelle tous les symboles ont les significations définies ci-dessus,
(viii) soumettre un composé obtenu par la réaction (vii), de formule (Ia-5) :



(Ia-5)

dans laquelle tous les symboles ont les significations définies ci-dessus, à une réduction,
(ix) faire réagir un composé obtenu par réaction (viii) de formule (Ia-6) :

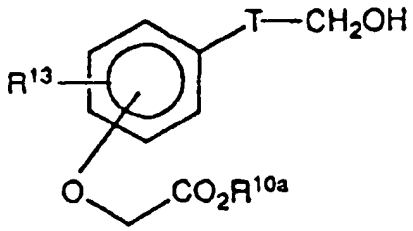


(Ia-6)

dans laquelle tous les symboles ont les significations définies ci-dessus, avec un composé de formule (h) :

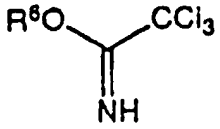
$$R^{3a}I \qquad (h)$$

dans laquelle R^{3a} représente un groupe alkyle en $C_{1\text{-}6}$ ou un groupe phényle,
(x) faire réagir un composé de formule (II) :



(II)

dans laquelle tous les symboles ont les significations définies ci-dessus, avec un composé de formule (i) :

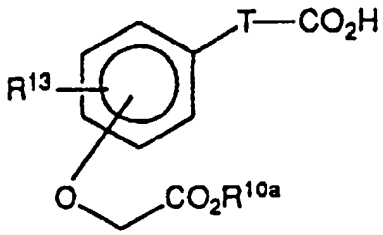


(i)

dans laquelle R^6 a la même signification que définie ci-dessus, ou avec un composé de formule (s) :

$$R^6X \qquad (s)$$

dans laquelle X représente un atome d'halogène et R^6 a la signification définie ci-dessus,
(xi) effectuer l'estérification d'un composé de formule (IV) :

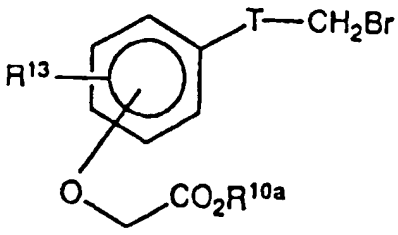


(IV)

dans laquelle tous les symboles ont les significations définies ci-dessus, avec un composé de formule (j) :

$$R^6OH \qquad (j)$$

dans laquelle R^6 a la signification définie ci-dessus :
(xii) faire réagir un composé de formule (IX) :



(IX)

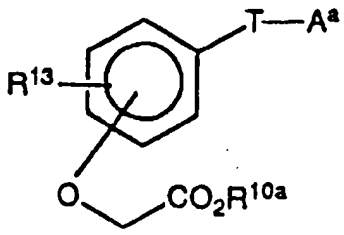
dans laquelle tous les symboles ont les significations définies ci-dessus, avec un composé de formule (q) :

$$HO{\sim}N{=}CR^7R^8 \qquad (q)$$

dans laquelle tous les symboles ont la même signification que définie ci-dessus, ou avec un composé de formule (r) :

$$HO\text{-}NH\text{-}CHR^7R^8 \qquad (r)$$

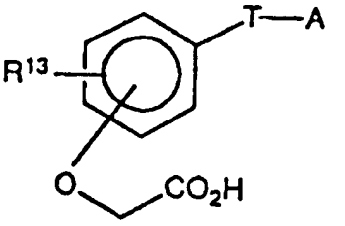
dans laquelle tous les symboles ont les significations définies ci-dessus,
(xiii) hydrolyser un composé obtenu par les réactions ci-dessus (i), (ii), (iii), (vi), (vii), (viii), (ix), (x), (xi) ou (xii) de formule (Ia) :



(Ia)

dans laquelle A^a représentei) $-CR^1{=}N{\sim}OR^2$,
ii) $-CHR^1\text{-}NH\text{-}OR^2$,
iii) -COE,
iv) $-CH_2NR^3\text{-}Y$,
v) $-CH{=}N\text{-}NR^3\text{-}CONR^4R^5$,
vi) $-CH_2\text{-}NH\text{-}NR^3\text{-}CONR^4R^5$,
vii) $-CH_2\text{-}NR^{3a}\text{-}NR^3\text{-}CONR^4R^5$,
viii) $-CH_2OR^6$,
ix) $-CO_2R^6$,
x) $-CH_2\text{-}O{\sim}N{=}CR^7R^8$ ou
xi) $-CH_2\text{-}O\text{-}NHCHR^7R^8$,

et les autres symboles ont les significations définies ci-dessus.
(xiv) estérifier un composé obtenu par la réaction ci-dessus (iv) ou (v) de formule (Ib) :

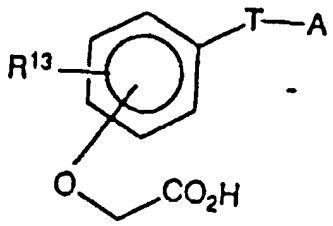


(Ib)

dans laquelle tous les symboles ont les significations définies ci-dessus, avec un composé de formule (o) :

$$R^{10b}OH \qquad (o)$$

dans laquelle R^{10b} représente un groupe alkyle en $C_{1\text{-}12}$,
(xv) effectuer l'amidation d'un composé obtenu par la réaction ci-dessus (iv) ou (v) de formule (Ib) :



(Ib)

dans laquelle tous les symboles ont les significations définies ci-dessus, avec un composé de formule (p) :

$$R^{11}R^{12}NH \qquad (p)$$

dans laquelle tous les symboles ont les significations définies ci-dessus, ou
(xvi) convertir un acide phénoxyacétique de formule (I) en son sel ou son sel par addition d'acide correspondant par un procédé connu, si souhaité.

14. Composition pharmaceutique qui comprend, comme ingrédient actif, une quantité efficace d'un dérivé d'acide phénoxyacétique de formule (I) décrit dans la revendication 1 ou l'un de ses sels non toxiques, ou l'un de ses sels par addition non toxiques, avec un véhicule ou un revêtement pharmaceutique.

15. Dérivé d'acide phénoxyacétique de formule (I) décrit dans la revendication 1, ou l'un de ses sels non toxiques, ou l'un de ses sels par addition d'acide non toxiques, pour une utilisation dans la fabrication d'une composition pharmaceutique pour la prévention et/ou le traitement de thrombose, d'artériosclérose, de cardiopathie ischémique, d'ulcère gastrique ou d'hypertension.